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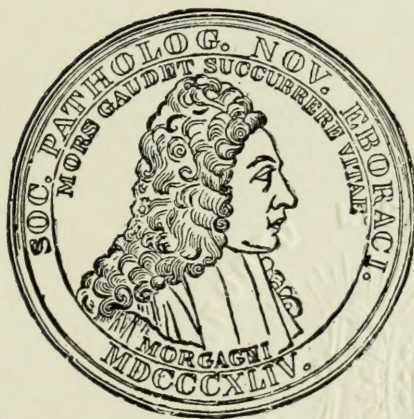


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DR. DOUGLAS SYMMERS, President.

EXPERIMENTAL RICKETS IN RATS

(Studies from the Department of Pathology, College of Physicians and Surgeons, Columbia University, New York)

Introduction: Since the fall of 1920, a group of workers in the Department of Pathology at Columbia, aided by a grant from the Commonwealth Fund, has been engaged upon a study of experimentally produced rickets in rats.* As you are aware, similar researches are being carried out at Baltimore and New Haven by McCollum, Shipley, Park and their associates, and more recently investigations along similar lines have been begun by McClendon and Baugness¹ at the University of Minnesota, and by Korenschevsky² at the Lister Institute.

Our own work has developed upon the basis of a chance observation.³ Professor H. C. Sherman, of the Department of Chemistry, had for a number of years been interested in the mineral metabolism of rats, and at our request, very kindly sent to us for examination some of the animals which had died during his experiments. Of these rats, some proved to be rachitic, others showed normal or merely osteoporotic bones; and on subsequent inquiry, it was discovered that the determining factor was the absence or presence of basic potassium phosphate in the diet. Here, then, was a simple and, as it proved, unfailingly reliable method for producing and preventing rickets under controlled experimental conditions.

Further work has followed logically and obviously enough from this basic observation. We have varied and modified the inorganic and organic constituents of this rickets-producing diet, so as to define as precisely as possible the essential and important factors in the production or prevention of the disease in rats.

* The organization of the work has been as follows: Director: Prof. J. W. Jobling. Chemistry: T. F. Zucker and M. Gutman. Diets and Care of Animals: G. F. McCann and M. Barnett. Experiments on Light and Fat-Soluble Vitamines: A. F. Hess, L. J. Unger, and M. Weinstock. Pathology: A. M. Pappenheimer. Radiography: Dr. Steiner and Miss Shaw. Technician: I. B. Tice, Jr. The following students have taken an active part in the experimental work: Mrs. Angus M. Frantz, Misses Stimson, Strauss, Stanley-Brown, Lichtenstein, Mrs. Silverberg, Messrs. Klein and Seidlin.

Other problems which have been taken up are the rôle of the fat-soluble vitamine A, the behavior of the inorganic blood phosphate on various experimental diets, and the effects of light and other forms of radiant energy, in the prevention of the experimental disease. A study of the curative principles of cod liver oil is also being carried out, and will be reported upon elsewhere.

By way of introduction to a more detailed presentation of these experiments, we may describe briefly the type of bone lesions seen on the typical diets; and it may be of interest also to trace the process of healing under the influence of cod liver oil. The ribs have been chiefly studied. The large number of animals used (over 800) has made a study of the long bones impracticable, but whenever this has been done, the changes in the ribs have been found to be a reliable criterion of the lesions in other bones.*

PATHOLOGY

High Calcium-Low Phosphate Diet (Diet 84): On this diet, histological changes identical in all details with those of human rickets have been invariably found. The lesions may be summarized as follows:

Resting cartilage—unchanged. Zone of preparatory calcification greatly increased. Normally this is composed of not more than five to six cells; in the rachitic animals on this diet, it may be 50 cells or more in depth. The cartilage is continued in the form of irregular prolongations into the diaphysis. The matrix is wholly calcium-free, except for the extreme tips of the prolongations. Osteoid is present in great excess both at the metaphysis and on the periosteal and endosteal surfaces of the cortex, where it may lead to great reduction in the size of the marrow cavity. Infracctions, with large masses of calcium-free cartilaginous and osteoid callus, are of frequent occurrence. The calcified cortex is reduced in width and in places interrupted. There is often great angular deformity and swelling at the chondro-costal junction. (Fig. 2.)

* The bones were decalcified for 5 days in Mueller's fluid, stained with hematoxylin-eosin, and silver nitrate-safranin. The progress of the bone lesions in each case has been followed by radiographs.

High Calcium, and Phosphate Adequate for Bone Growth
(Diet 85): On this diet, deficient in the character of the pro-

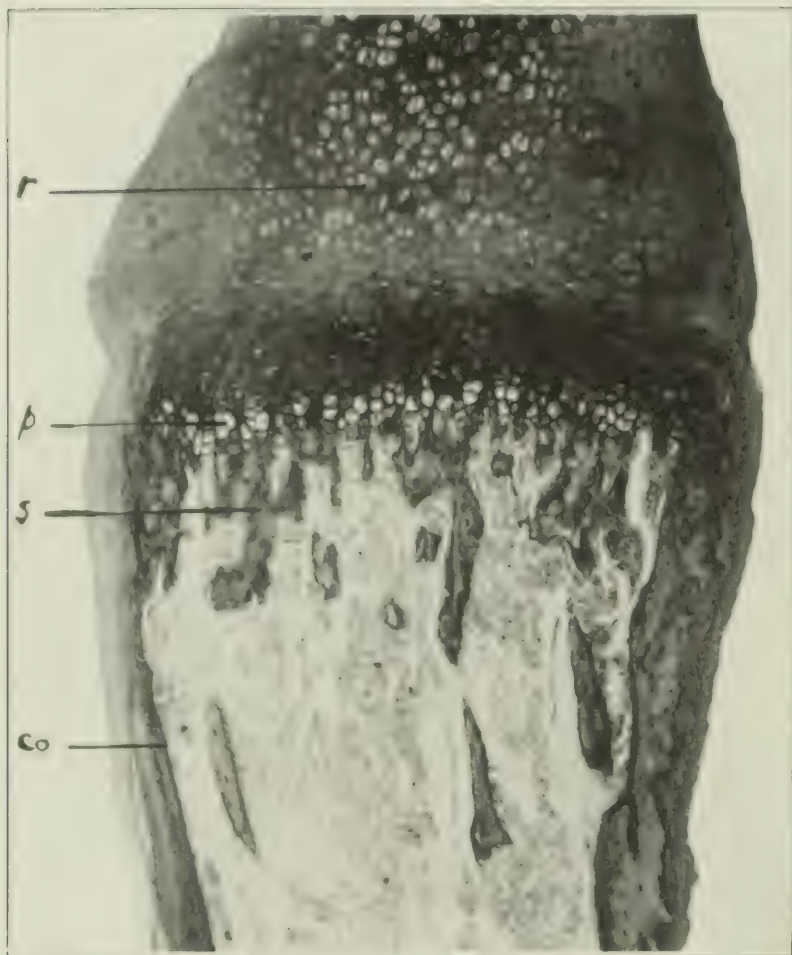


FIG. 1. Rat 38. Full diet. Normal rib. Zone of preparatory calcification (*p*) does not exceed three cells in depth. Matrix calcified. Trabeculae of spongiosa (*s*) show orderly parallel arrangement. No osteoid margin is visible.

teins, in the fat-soluble vitamins, and in its mineral constituents, other than Ca and PO_4 , growth is unsatisfactory. Examination of the bones shows no rachitic changes, but there is simple osteoporosis without rickets. The zone of preparatory calcification is reduced to three or four cells, the matrix is completely calcified. Endochondral osteogenesis is imperfect, the trabeculae of the primary spongiosa being sparse and poorly formed. The bony cortex is thin, and the marrow cavity wide. There is no excess of osteoid, and an osteoid border is rarely seen about trabeculae or cortex.

High Phosphorus-Low Calcium Diet (Diet 85 C): This diet, as has been pointed out also by the Johns Hopkins workers,⁴ leads to an atypical form of rickets. The following features differentiate this type of bone changes from that produced by a high

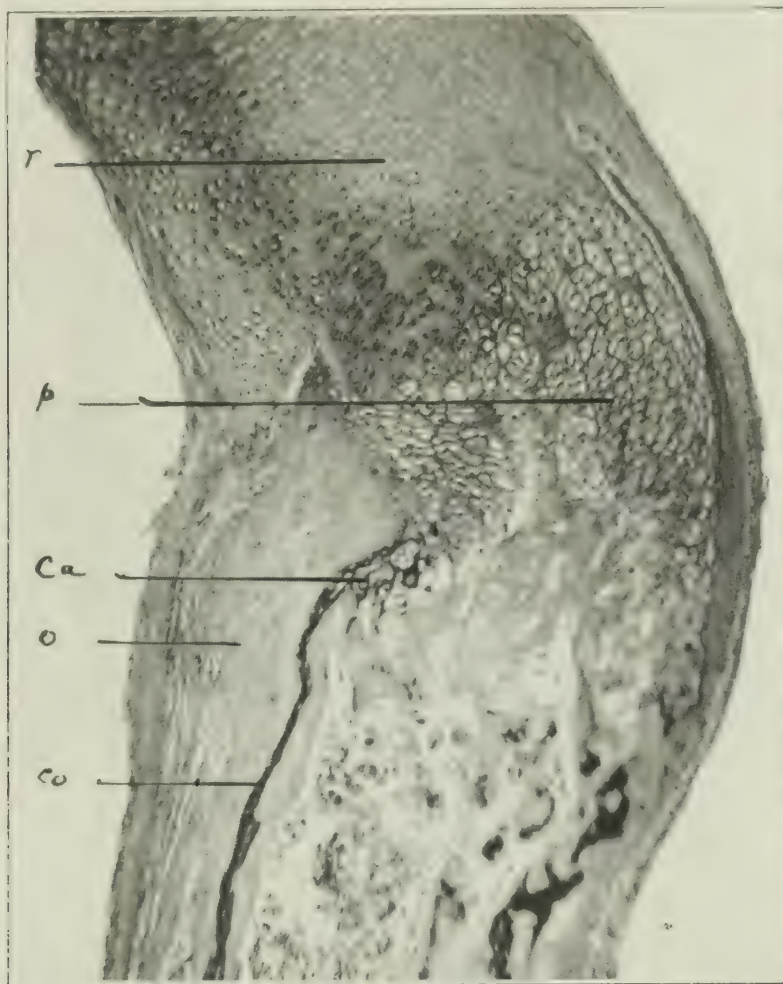


FIG. 2 Rat 246. 34 days on Diet 84 (high calcium-low phosphorus). Advanced typical rickets. Zone of preparatory calcification very deep and irregular, entirely Ca-free (*p*), except at extreme tip (*ca*). Great excess of subchondral and cortical osteoid (*o*). Calcified cortex reduced in width (*co*).

calcium-low phosphorus diet. The zone of preparatory calcification is but slightly greater than in normal ribs, and in some cases does not exceed 5 or 6 cells. The calcium depositions in the matrix are more abundant than on Diet 84, though usually limited to the distal portion of the cartilage. In the subchondral zone, which unlike the typical rachitic metaphysis is free from

metaplastic cartilage, are broad trabeculae, composed almost wholly of calcium-free osteoid. The cortical osteoid is moderately increased, and infractions are present. The calcified cortex is reduced in width, and is more readily decalcified than in diets containing an adequate amount of calcium. In general, there

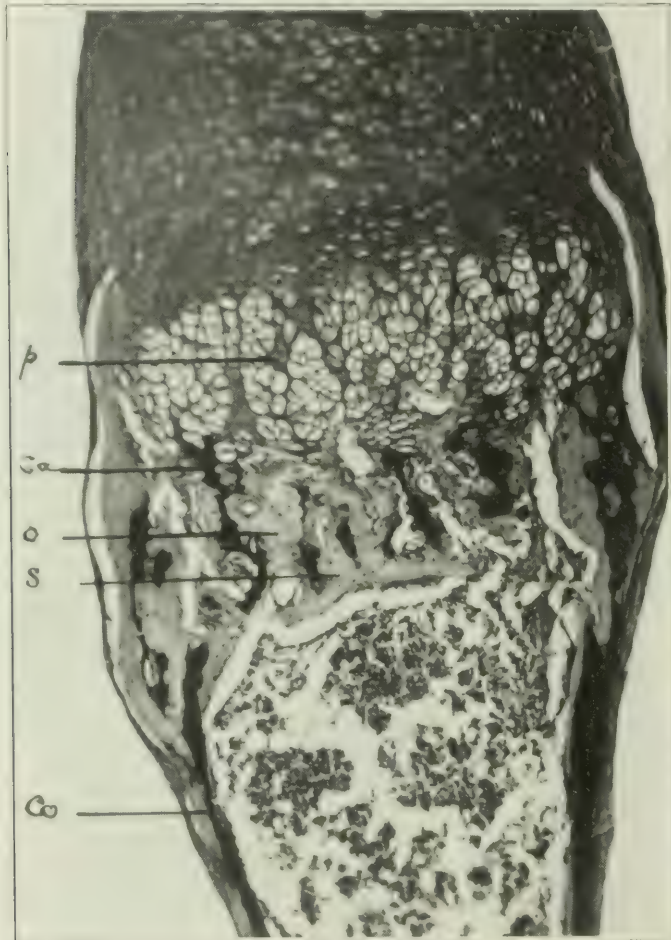


FIG. 3. Rat 495. 39 days on Diet 85-C (low calcium-high phosphorus). Zone of preparatory calcification (*p*) 9 to 12 cells deep, fairly regular columnar alignment, calcium deposition limited to prolongations of matrix into spongiosa (*ca*). Spongiosa (*s*) composed of stout osteoid trabeculae extending only a short distance towards diaphysis. Cortical osteoid slightly increased. Marrow cavity wide. Note absence of marked swelling and deformity at chondro-costal junction.

is little swelling or deformity at the chondro-costal junction. (Fig. 3.)

Deficiency of Both Calcium and Phosphorus (Diet Q): This

diet only exceptionally leads to a simple osteoporosis, the conditions commonly found being intermediate between those of osteoporosis and rickets. In the radiograph, the defect at the upper extremity of the tibia is much narrower than in the typically rachitic rat, and the swelling and deformity are negligible. Infractures, however, do occur and the bones are delicate and fragile, rather than pliable.

Histologically, the zone of preparatory calcification is increased in depth, but not to the same degree as on Diet 84. Calcification of the matrix is either absent or limited to the distal portion and to the short prolongations into the diaphysis. There is moderate increase in the osteoid of the spongiosa and cortex—less extreme, however, than on Diet 84. No clear evidence of increased osteoclastic resorption was found. The detailed descriptions of the lesions obtained with other variously modified diets must be left for final publication.

Healing Under Influence of Cod Liver Oil: We owe to Shipley, Park, McCollum, and their co-workers,⁵ the demonstration that the rickets of rats, like that of human beings, is definitely benefited by the administration of cod liver oil. The deposition of calcium in the rachitic metaphysis of the tibia under treatment is so clearly evident in the radiograph that it affords a convenient and reliable biological test of the activity of this substance. Park has excellently described the histological changes in their earlier stages. We shall not take the time to cite his work in detail, but shall try to give a brief description of the healing process as we have observed it in our own animals. Our studies are still incomplete, but the material which has already accumulated is sufficient to give a fair idea of the main features which mark the restitution of the rachitic bone to an approximately normal condition under the influence of this agent.

On Diet 84, the cartilage throughout the zone of provisional calcification is virtually Ca-free. Rarely at the extreme tip of the irregular prolongations of the cartilage into the metaphysis, one may find a small amount of calcium. The first detectable effect of the administration of the cod liver oil, or one of its active fractions, is the deposition of calcium phosphate in this

zone of preparatory calcification. The exact site of its deposition varies somewhat, but it is apt to appear first in the lateral portions of the cartilage. Somewhat later, it may extend transversely across the cartilage as a broad band. Gradually the area of calcification extends, but two facts should be noted. First, the basal cells, which are apt to retain more or less of their columnar arrangement, have no calcium about them; and secondly, areas in which the cartilage appears to be necrotic also become calcified with difficulty.

The time relations vary with the dosage, and probably also with the severity of the rachitic lesions at the time when treatment is begun. We have observed a deposition of Ca in the cartilage within twenty-four hours after a single dose of five drops, and after five to seven days calcification is often present throughout the greater portion of the cartilage. The complicated rearrangements necessary to bring about a complete return to the normal require, however, a considerably longer period.

Accompanying this deposit of calcium in the matrix of the cartilage, there is a laying down of the salt also in the osteoid tissue. In the perichondral osteoid, which is always very considerably thickened, one finds a granular deposit beginning in that portion of the osteoid contiguous to the cartilage. The granules of calcium are ranged often in linear rows at right angles to the cartilage, like minute stalactites. In the trabeculae of the spongiosa and in the osteoid masses, which envelop the calcified bone of the cortex, new calcium is deposited, at first in loose granular form, or as seen in hematoxylin-eosin preparations, as a faint purple cloud, fringing the originally calcified bone. As this osteoid tissue becomes transformed into fully calcified bone, the osteoblasts embedded in its substance change their character, becoming more angular, pyknotic, and acquiring the filamentous processes characteristic of adult bone corpuscles. The deposit of the calcium always begins in that portion of the osteoid which is adjacent to the originally calcified bone, so that one of the earliest and most characteristic indications of active calcification is the wiping out of the sharp line of demarcation between the calcified bone and the osteoid border.

The active deposition of calcium in the cartilage and osteoid is very easy to demonstrate and to understand, at least from the morphological point of view. But the return to the normal involves also a resorption of the excessive cartilage and osteoid tissue which make up the swollen rachitic metaphysis, and there are details in this process which are less easily analyzed.

The excess of cartilage appears to be disposed of in the following way. Following the calcification of the matrix, the cartilage cells are invaded on all sides by blood vessels and polygonal mononuclear cells in exactly the same fashion as takes place normally at the epiphyseal junction; the only difference being that this opening up of the cartilage cells is most irregular. With the disappearance of the cells, there remains for a time the calcified matrix, in the form of curved rods which are destined to form the scaffolding for new bony trabeculae.

The removal of the excess cartilage, therefore, involves no new principles. It is apparently conditioned by the calcification of the matrix, just as in normal endochondral growth. The resorption of the osteoid tissue, which undoubtedly occurs also on a large scale, is less easy to follow. We have observed that at this stage, the osteoid tissue still present in the subchondral region stains less intensely, has a looser, more fibrillar texture, and often seems frayed-out at the margins as if it were undergoing solution. Occasional multinucleated cells may be found, but osteoclastic resorption seems to play a little part in the process. Possibly further study with differential stains will add details to our understanding of this process, but the interpretation of the finer changes underlying bone resorption has always been a matter of difficulty.

However brought about, this resorption of the excess of osteoid very clearly takes place first in the proximal half of the rachitic metaphysis,—that is, the portion nearest the cartilage, and only later affects also the distal portion. (Figs. 4, 5.)

Accompanying the removal of the excessive cartilage and osteoid there takes place also an extreme and striking distention of the blood sinuses. Whether or not we assign to the blood vessels an active rôle in the resorption of the cartilage and osteoid,

this extreme vascularity is certainly one of the most characteristic and striking features of the healing process. Some of our preparations show very clearly also the penetration of the cartilage with blood vessels, which grow in from the perichondrium, at a level just beyond that which will form the new epiphyseal line. Schmorl⁶ has shown that these endochondral blood channels anastomose with those in the subchondral zone, and that they play an important directive part in the healing process.

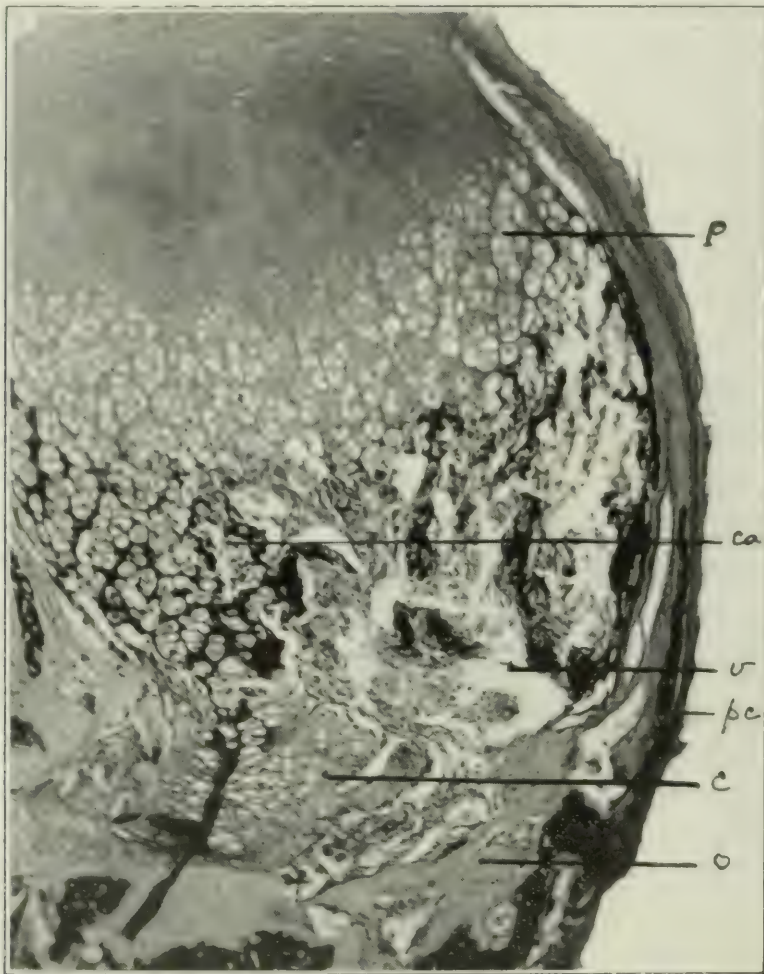


FIG. 4. Rat 549. 39 days on Diet 84. During the last ten days, received 1 drop of cod liver oil daily. Rib shows healing rickets. The zone of preparatory calcification is being reduced to average width of 10 cells (*p*), the prolongations of the cartilage show dense calcification of matrix (*ca*), and the cells are being invaded by wide blood sinuses (*v*). There is fresh Ca deposition in perichondral osteoid (*pc*). Much uncalcified osteoid is still present in the distal portion of the rachitic metaphysis (*o*).

We have not followed the healing process beyond this stage. It is clear, however, that the new epiphyseal line is reconstituted at the base of the cartilage by the resorption of the cartilaginous and osteoid metaphysis; and that this resorption is initiated by the deposit of calcium in the matrix of the cartilage, and to a lesser extent in the osteoid itself, and accompanied by great dilatation of blood vessels. The interesting problem of the mode of action

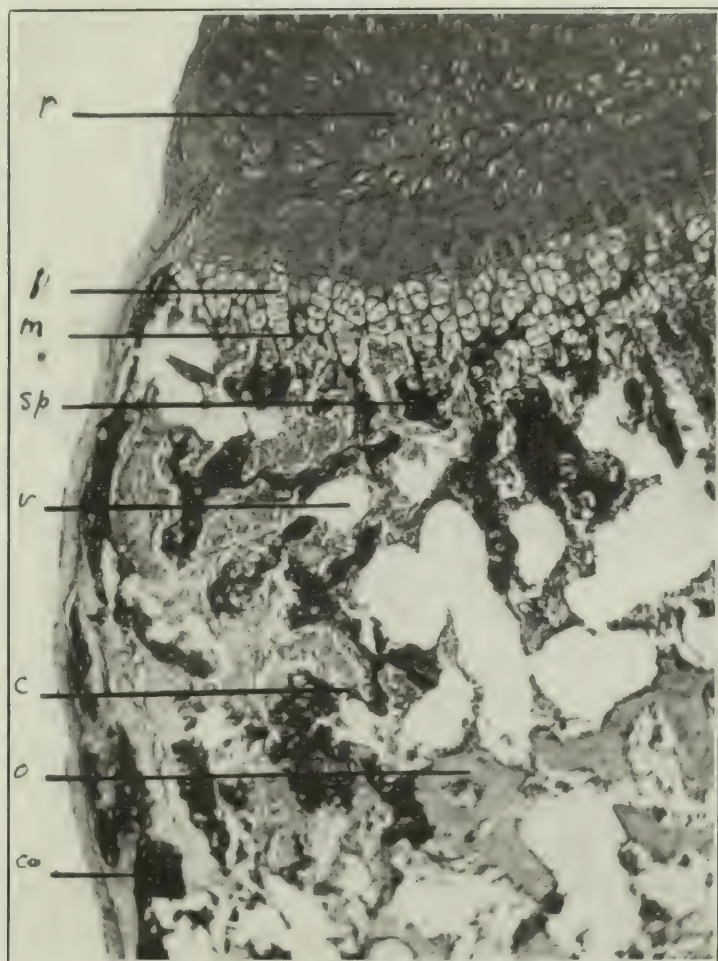


FIG. 5. Rat 474. 63 days on Diet 84. Treated 4 weeks with daily dose of 3 drops of cod liver oil. Rickets—late stage of healing. The zone of preparatory calcification is reduced to 6 cells or less, the matrix being calcified between the distal 2 or 3 cells. A few nests of cartilage cells still remain in the depths of the original metaphysis (*c*), the remainder having been resorbed. They are surrounded by densely calcified matrix. A new and very irregular spongiosa has been formed (*sp*); the trabeculae in the subchondral zone are completely ossified, but osteoid tissue is still found in the distal portion of the metaphysis (*o*). The blood sinuses are enormously dilated.

of this curative agent may thus be defined as follows: how does cod liver oil bring about this deposition of calcium in the cartilage and osteoid? The later phases of the healing processes, as we have seen, follow upon this preliminary calcification along the lines observed in normal bone formation. It is the initial step which requires explanation.

THE EFFECT OF VARYING THE INORGANIC CONSTITUENTS

The rickets-producing Diet 84, described by Sherman and Pappenheimer,³ has served for the basis of the following studies. Over 150 rats have been kept upon this diet for periods of three to five weeks, and in every case rickets has developed. The protective action of potassium phosphate has also been confirmed by the use of Diet 85. (See table.) More than 50 rats have

TABLE I

<i>Diet 84</i>		<i>Diet 85</i>	
Patent flour	95.	Patent flour	95.
Sodium chloride	2.0	Sodium chloride	2.0
Ferric citrate	0.1	Ferric citrate	0.1
Calcium lactate	2.9	Calcium lactate	2.5
		Basic potassium phosphate (K_2HPO_4)	0.4

now been given this diet and in no case has rickets developed.

Determination of the Rôle Played by Potassium and Phosphate Ions, Respectively in the Protection Given by Basic Potassium Phosphate: Secondary sodium phosphate in the proportion of 0.8 per cent. of the diet was substituted for the secondary potassium phosphate in Diet 85, this amount being calculated to contain an equivalent amount of phosphorus (.072 mgm.). Of four rats on this diet none developed rickets.

For another group of three rats 0.35 per cent. of potassium chloride was used, thus adding an equivalent amount of potassium to the diet in the form of chloride instead of phosphate. These rats all developed rickets in as severe a form as did control rats on Diet 84.

It is obvious that the protective effect of basic potassium phosphate is due to the phosphate and not the potassium ion.

Determination of the Amount of Phosphate Necessary to Protect

Rats were placed upon diets in which graded amounts of basic potassium phosphate had been substituted for equivalent amounts of calcium lactate in Diet 84. Additions of 10, 25, and 50 mgm. per cent. of phosphorus were made in this way. Of the three rats receiving 50 mgm. per cent. of added phosphorus, one showed no evidence of rickets. The other two showed slight or early lesions.

The rats receiving 10 and 25 mgm. per cent. of added phosphorus all showed definite rachitic lesions.

Since Diet 85 which contains 72 mgm. per cent. added phosphorus affords complete protection against the development of rickets, the protective level of phosphorus in this particular series of diets is seen to lie between 50 and 75 mgm. per cent. added to the original rickets-producing diet.

Modification of Inorganic Constituents other than Calcium and Phosphorus

Five rats were given a diet composed of flour and 5 per cent. of a salt mixture prepared similarly to that described by Osborne and Mendel except that no phosphoric acid was included. These rats all developed marked rickets.

This salt mixture as given contains an amount of calcium approximately equivalent to that in Diet 84, and it also contains sodium, potassium, magnesium, iron, iodine, fluorine, chlorine, manganese, and aluminium in the amounts considered necessary for adequate growth, with the single exception of phosphorus. The development of rickets in these rats would seem to indicate that these other elements have no protective action.

The sodium chloride content of Diet 84 is 2 per cent. In another experiment this was reduced to 0.5 per cent. Three rats on this diet developed typical rickets, showing that excess of sodium chloride is not a factor in the production of rickets by Diet 84.

Effect of a Deficiency of Ca in the Presence of an Excess of Phosphate

The diet used in this experiment, Diet 85-C, has the following composition:

	Per cent.
Patent flour	95.0
Sodium chloride	2.0
K ₂ HPO ₄	2.9
Ferric citrate	0.1

Rats on this diet have all shown lesions which are considered to be those of an atypical rickets. These lesions have been discussed in the introductory portion of this paper.

Effect of a Deficiency of Both Ca and PO₄

The diet used for this study was composed of:

Patent flour	97.9
Sodium chloride	2.0
Ferric citrate	0.1

It is deficient in both Ca and phosphate, the calcium being estimated to be 0.018 mgm. per cent. as compared with 0.553 gms. per cent. in Diet 84. The P content is approximately .088 per cent. or five times that of the calcium. Of eleven rats on this diet, nine have shown lesions which are similar to those produced by the high phosphorus, low calcium diet described above, while the remainder have developed an osteoporotic condition of the bones.

Effect of Phosphate Deficiency upon the Bones of Adult Rats

Three rats after 126 to 182 days of normal growth upon normal diets were placed on Diet 84. One rat was kept on the deficient diet for ten days, the other two for forty-two days. They all showed practically identical lesions. The zone of preparatory calcification was very narrow. There was a definitely increased osteoid margin about the trabeculae of the spongiosa and along the endosteal surface of the cortex. This osteoid was

bordered by distinct osteoblasts. The calcification of the cartilage remained unimpaired.

MODIFICATIONS IN THE ORGANIC COMPONENTS

It seemed desirable to study the following questions:

1. Is phosphorus, ingested in organic combination, of equal value as compared with inorganic phosphorus, for the purposes of bone formation?
2. Do the water-soluble and fat-soluble vitamins exert any protective or curative effect, aside from the phosphorus content of the substances in which they occur?
3. Is it possible to produce rickets on a diet more nearly adequate for proper nutrition and growth than Diet 84?

Effect of Addition of Casein to Diet 84

In order to study the effect of phosphorus in the form of phospho-protein, three diets were used in which 5, 10, and 15 per cent. of casein was substituted for the same amounts of flour in Diet 84. The casein used was the ordinary commercial product which had been extracted with cold alcohol by slow percolation until the washings were colorless, and then extracted for forty-eight hours with two changes of ether. The diet containing 10 per cent. of casein has a P content of 162 mgm. per cent. or approximately that of Diet 85. The diet containing 15 per cent. of casein had a phosphorus content well in excess of the protective level found for diets containing inorganic phosphates.

Three rats were placed on each of the three diets. All nine showed signs of definite rickets in x-rays taken on the 22nd to 28th days. One rat on the 10 per cent. casein diet and one on the 15 per cent. diet killed at this time showed definite rickets, but in the former there were evidences of early healing.

The other four rats which were receiving these two diets showed complete or partial healing of the lesions at 35 to 37 days. The rats on the 5 per cent. casein diet, a diet well below the previously determined level of protection by the Na and K phosphate, all showed definite rickets after 28 days with no signs of healing.

From this it is concluded that the protection afforded by casein is not wholly equivalent to that given by the same amount of phosphorus in the form of basic potassium phosphate.

Effect of Addition of Lecithin

Three rats were given a diet similar to Diet 84, except that 2 per cent. of the flour was replaced by an equal weight of commercial lecithin. This amount of lecithin contained about 79 mgm. of phosphorus, the diet thus having a phosphorus content equal to that of Diet 85. The three rats showed no evidence of rickets either by *x*-ray or microscopically, showing that phosphorus in the form of lecithin afforded protection equal to that given by basic potassium phosphate.

Effect of the Addition of Yeast

Yeast extract (Harris Yeast Vitamin) was added to the diet with the double purpose of ascertaining the influence of the water-soluble vitamine and of another phosphorus-containing compound. Two groups of two rats each were given diets in which 0.5 per cent. and 1.25 per cent. of yeast extract replaced equal weights of flour in Diet 84. The 0.5 per cent. was calculated to give 25 mgm. of extract per day (each rat ate about 5 gm. of the total diet per day) and added 21 mgm. per cent. of phosphorus to the diet. 1.25 per cent. added 52 mgm. per cent. of phosphorus to the diet. Twenty mgm. per day of a similar yeast preparation were found by Osborne and Wakeman⁷ to carry sufficient water-soluble vitamine for the growth needs of young rats so that even the 0.5 per cent. vitamine extract diet was ample in this respect. All the rats on these diets developed marked rickets.

In a preliminary experiment a larger amount of yeast vitamin was given, approximately 100 mgm. per rat, each day. These rats failed to develop rickets, but here the phosphorus added to the diet was in excess of that which had been previously shown to prevent rickets.

Effect of Addition of Egg Albumin

The phosphorus-free protein, egg albumin, was added to the diet in an attempt to improve the nutrition of the animals. Ten per cent. was substituted for flour in Diet 84. Three rats showed marked rickets after 26 to 28 days on this diet, and this addition did not strikingly improve their nutrition.

The Addition of Butter and Butter-Fat

This was of especial interest in view of the questions in regard to the rôle of the fat-soluble vitamin in rickets. Mellanby's views and experiments in support of this idea are well known.

Subsequent work has, in general, been unfavorable to this conception, and various authors have failed to produce rickets by diets deficient in fat-soluble vitamin, in monkeys, infants, dogs, rats, kittens, guinea pigs, or pigs.

Shipley, Park, McCollum, and Simmonds⁹ cite experiments in which a diet adequate in phosphorus but deficient in fat-soluble vitamin failed to produce rickets.

Four rats were given Diet 84, modified by the substitution of 5 per cent. of pasteurized butter for flour. This amount of the same brand of butter completely protected all control animals against keratomalacia and evoked a characteristic rise in the weight curve with cure of keratomalacia in two rats which had been maintained for a long time on a fat-soluble vitamin-deficient diet. The rats on Diet 84 plus 5 per cent. butter all showed marked rickets after 32, 43, and 43, and 45 days.

To three other rats, 0.4 gm. of fresh butter (made in the laboratory from raw cream) was given daily. These also showed typical though moderate lesions when killed after 28 to 30 days on the diet.

Two rats, previously made rachitic, were transferred to a diet containing 10 per cent. of raw butter fat, and three similar rats to a diet containing 10 per cent. of pasteurized butter fat. After eight to ten days on these butter fat containing diets, these rats were killed. All showed marked rickets with no evidence of healing although the general health of these rats was excellent.

The foregoing experiments seem to us to show that the fat-soluble vitamin, although present in sufficient quantity to prevent the usually accepted signs of fat-soluble vitamin deficiency, neither prevents nor cures rat rickets.

Effect of Adding Meat to Diet 84. Meat and Flour Diet

Three rats were fed for periods of 33 to 39 days on Diet 84, supplemented by the addition of chopped and dried round steak *ad libitum*. The growth on this diet was normal, and the bones of these animals showed a normal structure. This diet was adequate in both calcium and phosphorus.

Three rats were placed for a period of 35 days upon a diet of dried chopped steak and flour without the addition of sodium chloride, ferric citrate or calcium lactate. This diet was rich in phosphorus, contributed by the meat, but deficient in calcium. These rats developed lesions very similar to those described above as occurring in the other rats on diets low in calcium, but rich in phosphorus—lesions which are considered to be those of an atypical rickets.

Amplified Rachitic Diet

The following diet has produced rickets in the entire series of seventeen rats on which it has been tried.

	Per cent.
Patent flour	80.9
Egg albumin	10.0
Butter-fat	5.0
Salt mixture	4.1

The salt mixture furnishes the following constituents:

	Gm. per 100 Gm. Diet
KCl85
Na ₂ CO ₃85
MgCO ₃286
Ca lactate	2.00
Ferric citrate1

On this diet approximately normal growth is obtained for periods of nearly a month. The addition of 72 mgm. of phos-

phorus in the form of basic potassium phosphate causes growth to be normal for periods of six weeks and longer. This latter diet has a P content of about 140 mgm. per cent. which has been shown to be about on the borderline of protection,—at least for all the diets of our experiments. As would be expected, then, some of the thirteen rats have developed rickets on this diet, while others have not, although the growth has, in almost every case, been excellent. In many cases, the rickets has been most severe in the rats which have grown most rapidly.

OBSERVATIONS ON THE INORGANIC PHOSPHATE OF BLOOD IN EXPERIMENTAL RICKETS IN RATS

The work of Howland and Kramer¹⁰ on the level of the inorganic phosphate in the blood in human rickets led to the conclusion that during the period of active rickets in children the inorganic phosphate of the blood is reduced, and that during the process of cure either by sunlight or cod liver oil, the phosphate rises again to its normal level.

Since the experimental rickets produced in rats is comparable in most important respects to human rickets, it was thought of interest to determine whether the same changes in blood phosphate could be demonstrated in rats. In applying the blood phosphate work of Howland and Kramer to experimental rat rickets, we have obtained results which on the whole agree very well with those reported by them at a recent meeting of the Society of Biological Chemists.

Because of the small quantities of blood which can be obtained from the animals, it seemed advisable to do the determinations on whole blood rather than plasma, if possible. Experiments undertaken to show the relative distribution of the inorganic phosphate in plasma and whole blood indicate that the level of phosphate is practically the same inside and outside the cells, and is maintained at a very constant level from day to day. Therefore, as far as inorganic phosphate is concerned, it is immaterial whether the determinations are done on whole blood or plasma.

TABLE II

Inorganic Blood Phosphate of Rats on Various Diets
Mgms. P per 100 c.c. of blood

No.	Diet		No. of Rats	Determinations	Rickets	Blood Phosphate		
	Mgm. P	Mgm. Ca				Max.	Min.	Aver.
Normal	?	?	55	43	95% show none	8.2	5.1	6.2
84	86	550	40	18	Marked in 100%	4.9	2.0	3.2
D	72	380	10	7	Marked in 100%	5.3	2.3	3.4
85	160	550	7	2	Sl. osteoporosis	5.6	5.4	5.5
E	120	380	16	14	Sl. rickets in 20%	7.4	3.1	6.1
85-C	596	20	16	6	Atypical rickets	7.6	6.0	6.6
F	596	18	12	9	Sl. atypical rickets	9.8	6.5	8.5
G	520	380	3	3	Normal 100%	9.8	9.4	9.6

Table II shows the average figures for the inorganic phosphate in the blood of rats on rickets-producing, normal and high phosphorus diets. We find that in general the reduction of the inorganic phosphate in the blood runs parallel to the degree of severity of the rachitic lesions. It will be seen also that the blood phosphate of rats (on these rather specialized diets) may be greatly influenced by the level of phosphate intake. On normal diets the range is from 5.1 to 8.2, average 6.2, and on high phosphate intake a very wide range from 6.2 to 9.8.

The dividing line between rickets-producing and non-rickets-producing diets is, however, sharp. Rats on diets containing 86 mgm. per cent. phosphorus all develop rickets and the range of blood phosphate from 2.0 to 5.0 averages usually around 3.2 mgm. per 100 cc. of blood. When as little as 75 mgm. per cent. P is added the rachitic lesions fail to appear and the blood phosphate runs an average around 5.5 to 6 mgm.

The study of the inorganic phosphate of rats under light or cod liver oil therapy brings up several interesting points. As shown in Table III, one group of rats on Diet 84 (containing 86 mgm. per cent. P) was treated with light from a mercury vapor lamp, as a preventive measure. In almost every case, complete prevention was secured but the blood phosphate, while distinctly above that of the controls, was nevertheless in the upper range of rachitic blood.

TABLE III

Prevention and Cure of Rickets
Inorganic Phosphate as mgms. per 100 c.c. Blood

Diet	No. of Determinations	Treatment	Rickets	Blood Phosphate		
				Max.	Min.	Aver.
84	18	Untreated	Beading + to +++	4.9	2.0	3.2
84	10	Mercury vapor lamp	Beading - to +	5.4	2.9	4.1
84	8	Codliver-oil preparations	Calcification + to +++	5.9	2.4	3.95

This would seem to indicate that the rats can produce non-rachitic bone at a lower level of phosphorus intake under the influence of light than is possible without its presence.

Curative experiments with cod liver oil preparations show active calcification of cartilage going on while the blood phosphorus is still in the rachitic range. So we conclude that a definite deposition of calcium salts may occur before the blood phosphorus regains its normal level. We have as yet no experiments in which the rats were carried through till the healing process was complete, but if we can draw analogies from the work of Howland and Kramer on human rickets, we ought to find that when healing is complete the blood phosphate will regain and maintain its normal level. It seems, therefore, that calcification is not directly controlled by the level of the blood P. Experiments are now in progress to determine the nature of the relation between these two factors.

LIGHT FACTOR IN HUMAN AND EXPERIMENTAL RICKETS

ALFRED F. HESS, M.D.

As is well known, since rickets was first described there have been two different theories as to the etiology of the disease—the dietetic and the hygienic. It has been attributed to various faulty diets. On the other hand, some have thought it due to a lack of fresh air, others to a lack of exercise, still others to a lack of

light. This is the way the subject has alternated for perhaps over 250 years. One of the facts that has stood out prominently in regard to the etiology of rickets has been its marked seasonal occurrence. The condition in this regard is peculiar. In a series of four or five hundred autopsies Schmorl definitely showed that rickets occurred most markedly in the winter time, and that its curve of incidence gradually decreased, becoming lower in the late spring and still lower in the summer time. This has been the experience practically of all clinicians. This seemed a fact that might shed light on its etiology, so that a few years ago I attempted by means of the mercury quartz vapor lamp to prevent rickets by using ultraviolet light. These results were unsuccessful. On the other hand, if the diet were at fault, it might be that there was a seasonal change in the milk, which forms the main diet of children, and that the fodder of the cows might be the variable factor. An attempt to solve this aspect of the problem showed that it made no difference, as regards the incidence of rickets, whether infants were fed on dried milk which came from pasture-fed cows, or whether they were fed throughout the winter with the commercial dried milk. This study had the vitamin theory in view. There is just as much rickets among the children fed the special "pasture" dried milk as those fed the ordinary dried milk.

As you know, rickets occurs to a certain degree in over 50 per cent. of all infants, and if you include x-ray diagnosis the incidence is still greater. Two or three years ago Huldschinsky¹¹ in Berlin showed that by means of the ultraviolet light rickets could be cured. Last spring I tried the effect of sunlight. Cases that had developed rickets during the winter were given sunlight treatment in the early spring. They were placed from fifteen minutes to half an hour in the sunlight, being given increasing doses of this radiation. It was found in all cases that the rickets was definitely cured within a period of a month or two. This was evident clinically and by means of the x-ray. Following this favorable experience the same method was tried with rats. Rats were fed on the typical rachitic diet described by Sherman

and Pappenheimer. Although Diet 84 produces rickets in 100 per cent. of cases, it did not lead to rickets in rats given daily exposure to the sun of fifteen minutes to one-half hour.¹² This has been the experience of others.¹³ It was found that such exposure is about equivalent to doubling the amount of phosphorus in the food. In other words, the rickets-producing Diet 84 became practically equivalent to the rickets-protective Diet 85. You will remember that Diet 85 is Diet 84 with the addition of 75 mg. per cent. of phosphorus. If the sunlight is allowed to traverse glass, that is, if one constructs a glass box for the rats, and the light first passes through this window glass, practically no protection is afforded. Again, if the sunlight is reflected, only a slight amount of protection is afforded. This naturally led to the supposition that the ultraviolet rays play a large part in the effect. Accordingly we made use of the ultraviolet rays for rats. Radiation with the mercury vapor quartz lamp afforded complete protection. It takes about two minutes' exposure daily, at a distance of three feet, to accomplish this.

Another source of radiation used was the carbon arc lamp, the spectrum of which is very similar to that of the sun. This source of a light at a distance of three feet, when applied for three minutes, also afforded protection. In cases of scurvy light was of little or no value. We put guinea pigs on typical scorbutic diet and gave them the same amount of treatment with sunlight, but they developed scurvy just as readily as those kept in the dark.

It is impossible to state an explanation of this phenomenon. This work would suggest that light is just as valuable for the animal world as it is for the vegetable world, and we have not been considering it sufficiently in connection with disease. From the clinical standpoint it shows that if we are to get the effect of light it must act directly on the body, and that in solaria, where the light passes through glass, no benefit results in regard to the protection or cure of rickets.

CONCLUSIONS

Rats on diets high in calcium but low in phosphate develop bone lesions which are identical with those of human rickets. Rats on diets low in calcium and high in phosphate develop an atypical form of rickets in which there is a great increase in the amount of osteoid tissue in the subchondral zones, with only a slight increase in the number of cells of the zone of preparatory calcification.

On diets deficient in both phosphate and calcium, but in which the phosphate is present in relatively greater amount than the calcium, lesions similar to the atypical rickets described above are produced in most cases. Rarely lesions resembling osteoporosis are seen.

An attempt has been made to study the steps by which healing takes place under the influences of cod liver oil.

The effect of varying certain inorganic constituents of the low phosphate-high calcium diet was tried. It was found that the phosphate and not the potassium ion was responsible for the protection conferred by basic potassium phosphate.

On the type of diet used, rickets could be prevented by the addition of between 50 and 75 mgm. of P in the form of basic potassium phosphate to the rickets-producing diet,—all other factors remaining the same. The addition of various other inorganic salts did not prevent the development of rickets.

Adult rats also showed an increase of osteoid tissue when maintained on a diet low in phosphorus, but there were no endochondral changes.

The inorganic constituents were also modified. Casein did not wholly prevent the development of rickets, though the phosphorus added in this way was in excess of the amount needed for protection when given in the form of basic potassium phosphate. Lecithin protected when the 75 mgm. per cent. of P were added in this way. Yeast extract did not prevent rickets when the level of phosphorus was below the protective level—although water-soluble vitamine for growth could be given by much smaller amounts of extract.

Egg albumin did not protect. Butter and butter-fat carrying fat-soluble vitamin in amounts sufficient to prevent xerophthalmia and to promote growth did not prevent the rickets.

A diet has been used on which growth is maintained at an approximately normal rate during the experiment, and on which rickets is invariably produced.

The inorganic phosphate of the blood of rats rachitic and non-rachitic has been studied. The rachitic rats showed phosphates ranging between 2.0 and 5.0 mgm. per 100 c.c. of blood, while the rats receiving sufficient addition of P_2O_5 in the diet to protect them against rickets had phosphates of 5.5 to 6 mgm. per 100 c.c.

The blood phosphate in rats in which the development of rickets on a low phosphorus diet had been prevented by exposure to sunlight, or cured by cod liver oil, showed blood phosphates within the rachitic zone, although active calcification was occurring in the bones.

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Discussion:

DR. NORRIS: I would like to ask if the rats were white rats that were used in the experiments, and also if any sections were made of the skin after exposure, for the reason that it has been known for some time that sunlight

has an effect on the epidermal cells of the skin. Work has been done which shows that sunlight has an effect on certain diseases. Although I do not remember the special tumor, I am under the impression that one of Neusser's assistants in Vienna, Chovstek, has written an article which shows the curious relations that developed as a result of the exposure to light.

DR. WOOD: I would like to ask whether experiments have been tried to determine whether these rats show in the blood an altered distribution of phosphorus. It might be interesting to make a total analysis of the rats, both normal and rachitic, and of the rats under exposure to light, to see whether they simply redistribute their phosphorus. They may take it from one organ and put it into the blood or bone, and in that way merely redistribute the phosphorus, or they may, in the light-cured animals, make a more efficacious use of what phosphorus is given to them, and I believe that a total analysis of the phosphorus in the whole rat might give some clue as to whether the animal has stored the same, or whether he has redistributed the phosphorus in a different way.

DR. SCHWARZ: I should like to speak about twins who regularly become rachitic, and I should like to ask Dr. Hess if he has been able to protect them by sunlight. Another point is the seasonal occurrence of rickets. I think its high incidence in winter time has a great deal to do with it, and that children having nasopharyngeal infections and broncho-pneumonia very often become rachitic. Whether that starts the disease by upsetting the phosphorus or calcium or whatever the proportion was, I do not know, but that is a well known clinical fact.

DR. HESS: In this work white rats were used almost entirely. We have done some work with black rats; Professor Donaldson sent some from Philadelphia. The dosage was not made sufficiently delicate to tell whether there was any difference between the two. There may be some difference, but with the dosage of light we used both the white and black rats were protected.

As regards the pigment, there seems to me a very great difference of opinion as to its function. Some think that it has merely a protective function. Others think that it changes the short waves to long waves. Still others think it acts merely as a catalyzer. It was true that in some of these white rats the hair was a little darker. It took on a slightly yellowish color in the course of the sun treatment.

In answer to Dr. Wood, we have not analyzed the bodies of the rats for the total phosphorus. Of course most of the phosphorus is in the bone. The differences would be very small. The bones have more calcium phosphate, and that is where the calcium phosphate would be in the greatest measure. There might be a small difference.

As regards twins, there was one case where we used the sun treatment with twins and found it efficacious. I had one case some time ago, before this work came out, where I tried to cure twins, who, as Dr. Schwarz says, are especially liable to rickets, by adding a considerable amount of calcium lactate to the diet of one, and the child which got the large amount of calcium lactate was the one which developed the greatest amount of rickets. This is

explainable now, because we know that the phosphate is so much more important than the lactate.

In regard to how much the rôle of infection plays, Korenschevsky fed rats with bacteria, and was unable to produce any effect. This work on rickets was done with the idea of infecting rats, but the diet in this case was not controlled.

DR. PAPPENHEIMER: May I say one word about the question of infection? We have had seven or eight hundred rats under observation, and there has been ample opportunity for contact infection. We have never seen one case of rickets develop which could be regarded as probably due to infection. That is, in all cases the appearance or absence of rickets was directly traceable to the diet. The only way that infection might enter into the question would be that certain diets predispose to infection, as the lack of fat-soluble vitamins predisposes to keratomalacia. That is a theoretical possibility, but since we found rickets to occur on diets in which the only deficiency was phosphorus alone, we should have to assume that phosphorus-deficiency alone would predispose to infection. If so, it predisposes only to this particular infection. Though the proof is not final nor absolute, everything points against the infective origin of these lesions.

I might add in regard to what Dr. Wood said that experiments such as he suggested have been planned, and we hope to get some light on the question of distribution of phosphorus.

DR. SCHWARZ: I do not think from what we know of the clinical picture in rickets that it is only a disease of the bones. It is a disease of the entire body. I think Aschenheim showed that the calcium content is diminished in the muscle and in the brain. I am a little bit at sea as to whether you really have in these rats rickets which is comparable to that in a child. There is no question of the way in which cod liver oil helps. I should like to see some work on the various organs of these rats to get the chemical composition of the entire rat.

I think Dr. Hess and Dr. Pappenheimer must have misunderstood what I said about infection. I do not think infection will cause rickets. I know, however, that anything will cause rickets in a child which makes the child ill. When a child is not in good general shape for some reason or other it will develop rickets, and I think if you look carefully the percentage of rickets in New York City would be about 80 or 90 per cent. You will find some clinical sign of rickets in nearly all children. Almost anything will turn the balance of calcium and phosphorus. What does it, we do not know, but infection certainly does it with a great deal of regularity.

ANALYSIS OF THE FINDINGS OF EIGHT ADDITIONAL EXAMPLES OF BUNDLE BRANCH LESIONS IN THE HEART

LOUIS FAUGERES BISHOP, M.D.

(Consultant Cardiologist to the Lincoln Hospital, New York)

Since presenting to the New York Pathological Society twenty examples of bundle branch electrocardiograms which were published in the PROCEEDINGS, I have collected eight additional examples from about five hundred consecutive patients.

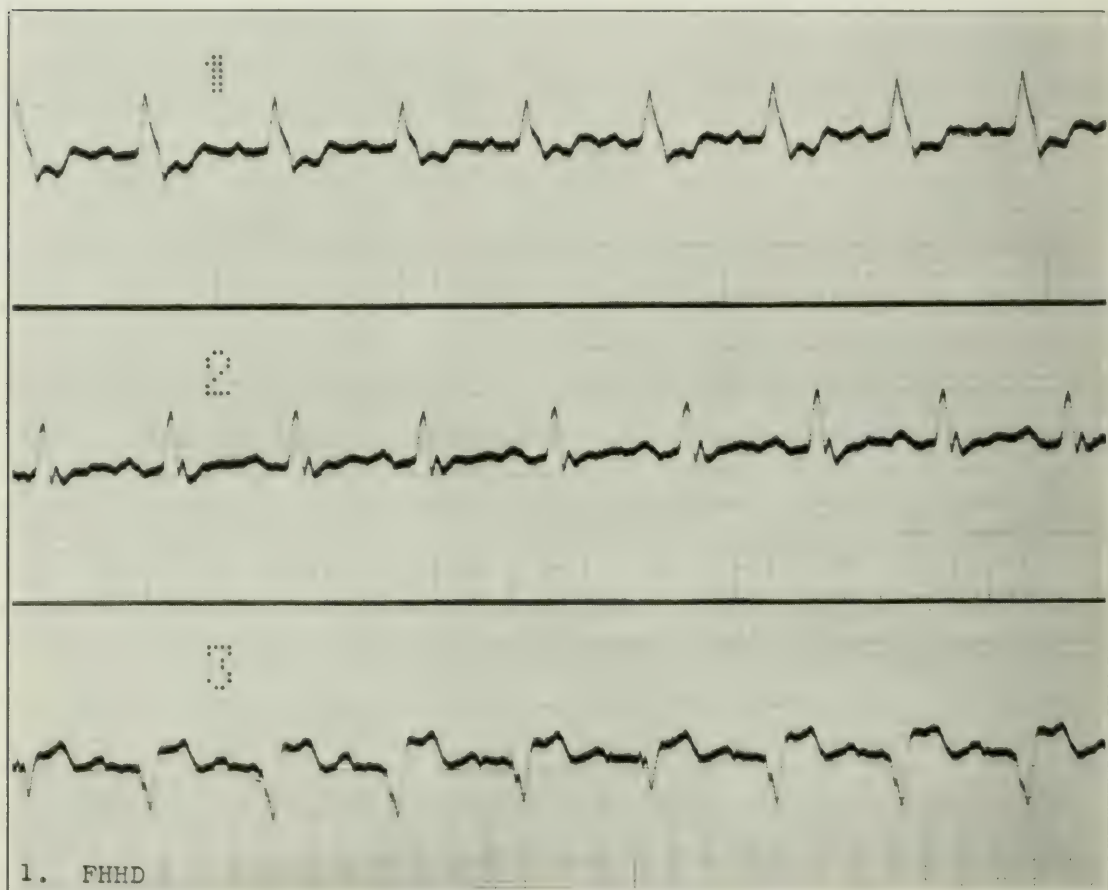


FIG. 1

This shows a frequency of 1.6 per cent. which is about the same as in the previous group. One of the eight cases is particularly interesting in that the records taken two and one half years previously showed the electrocardiogram to be normal.

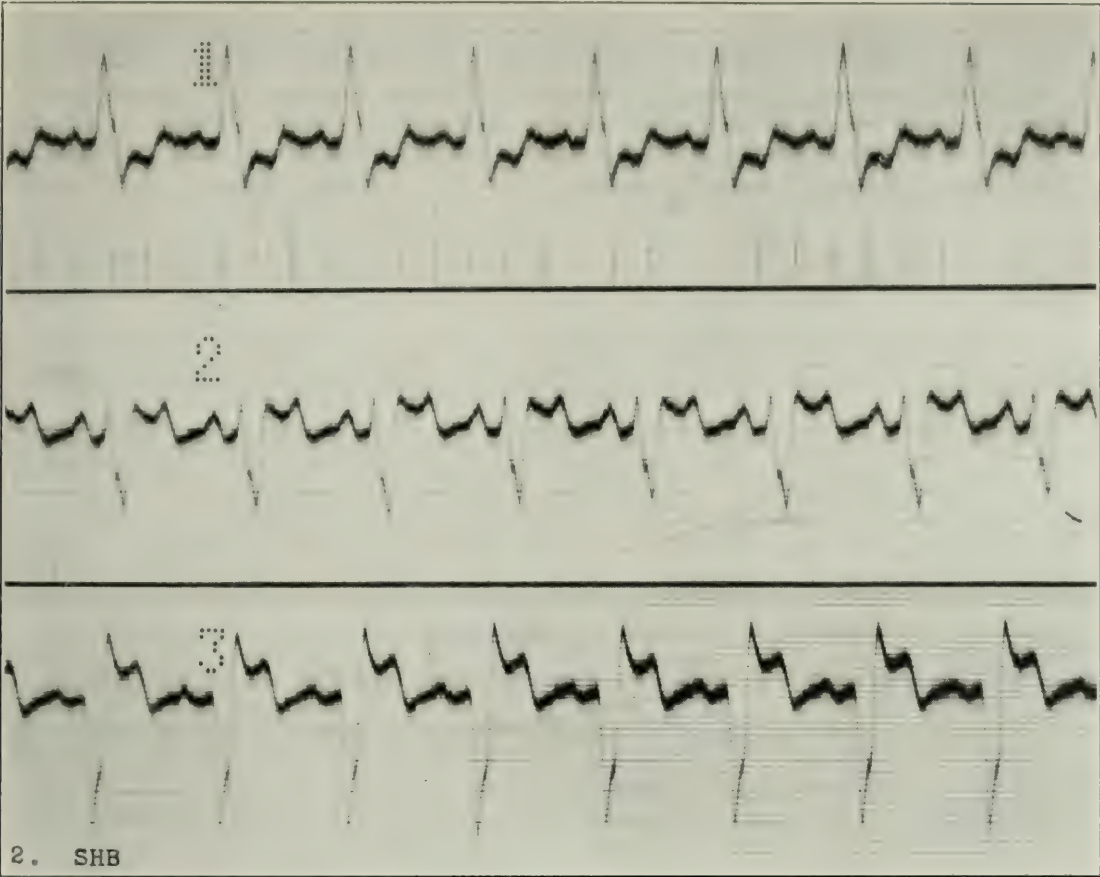


FIG. 2

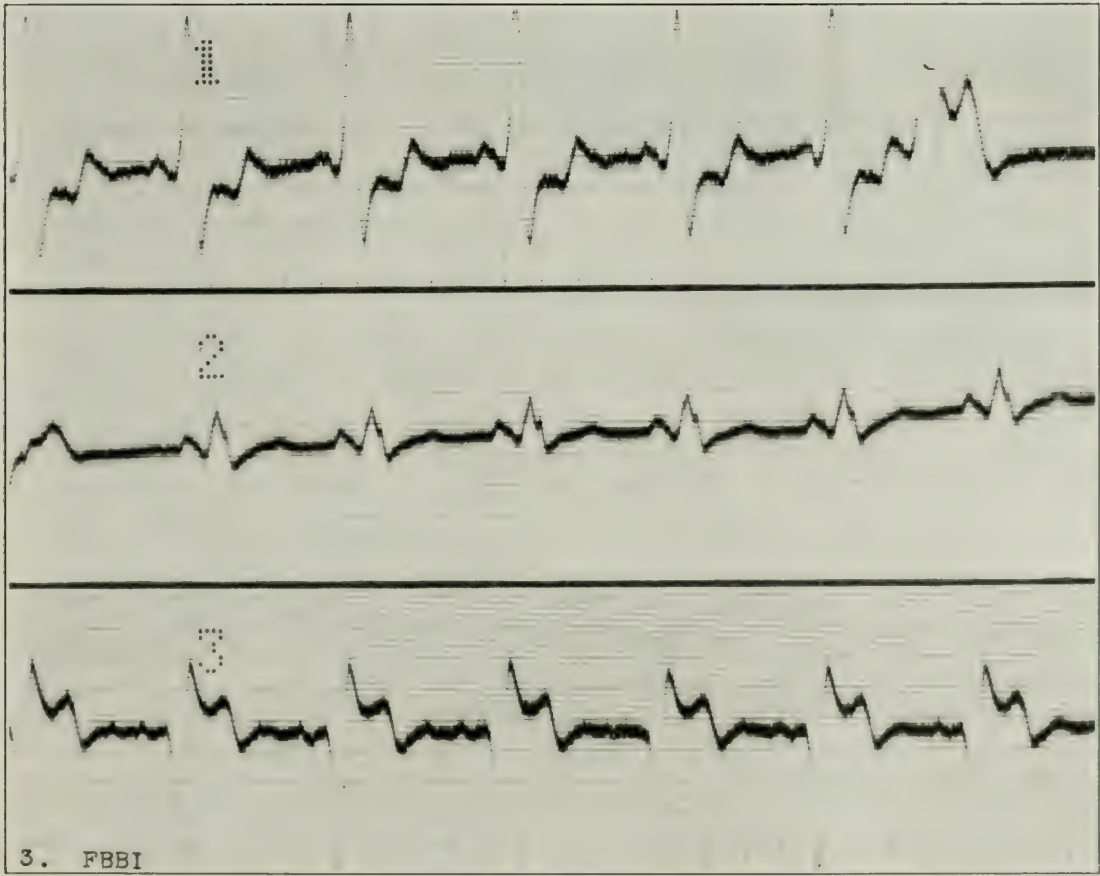


FIG. 3

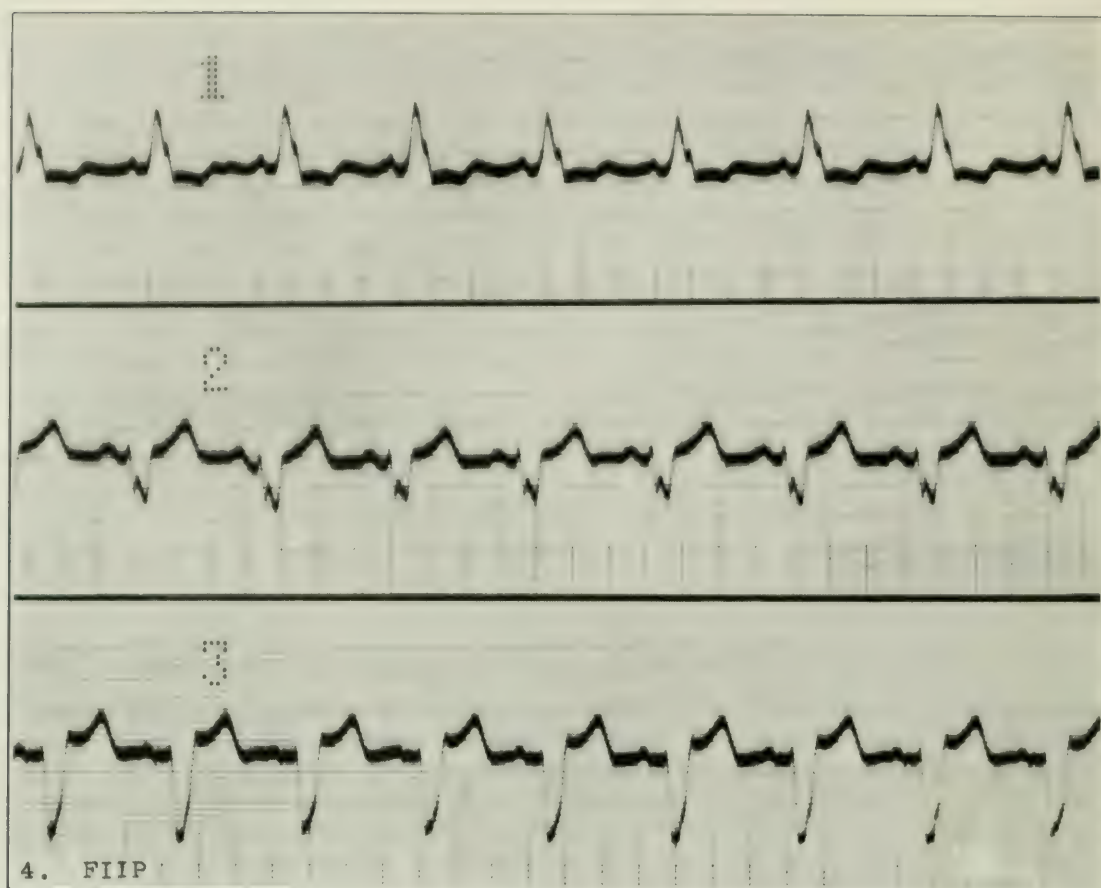


FIG. 4

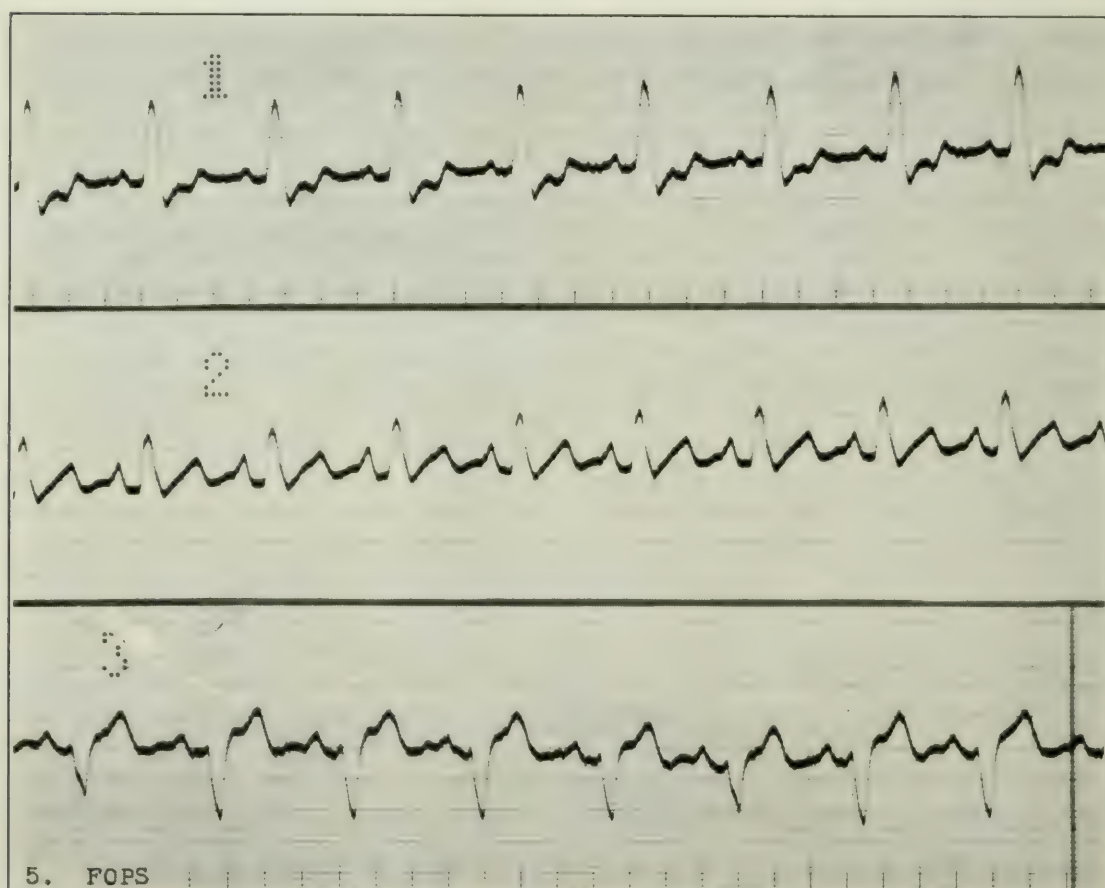


FIG. 5

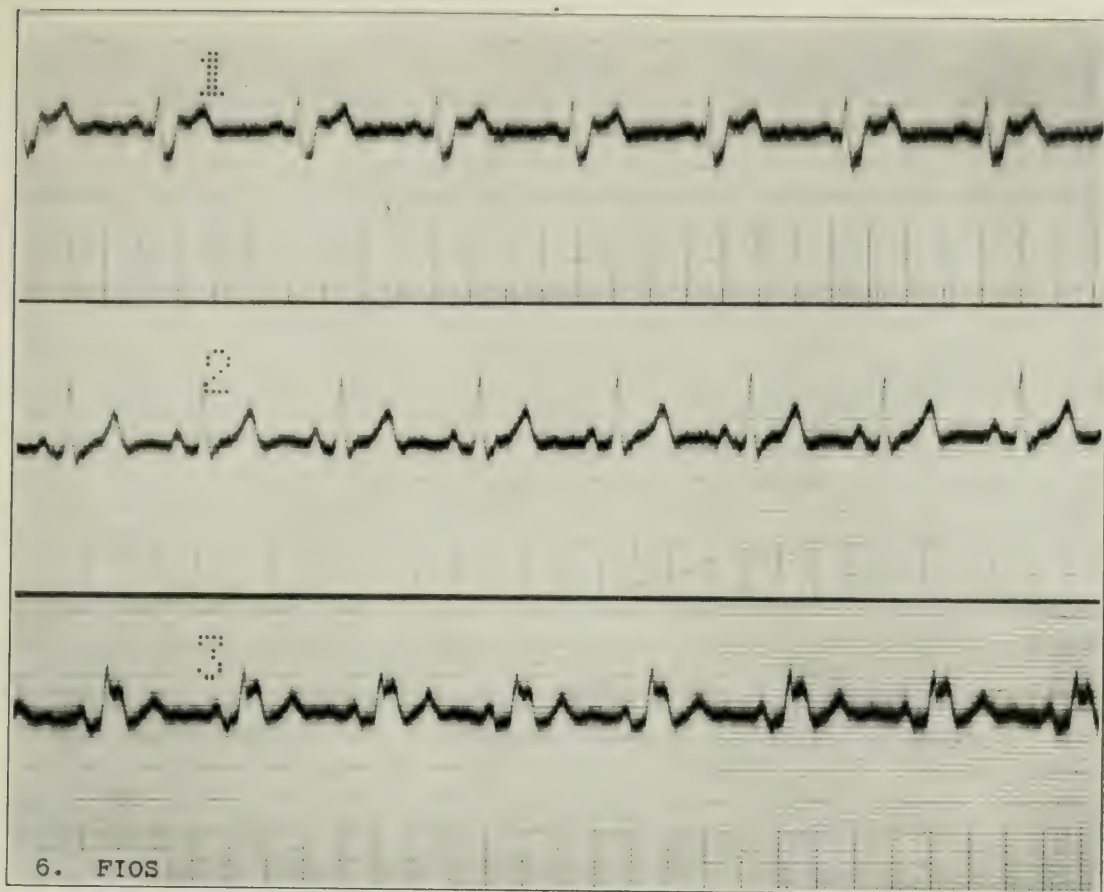


FIG. 6

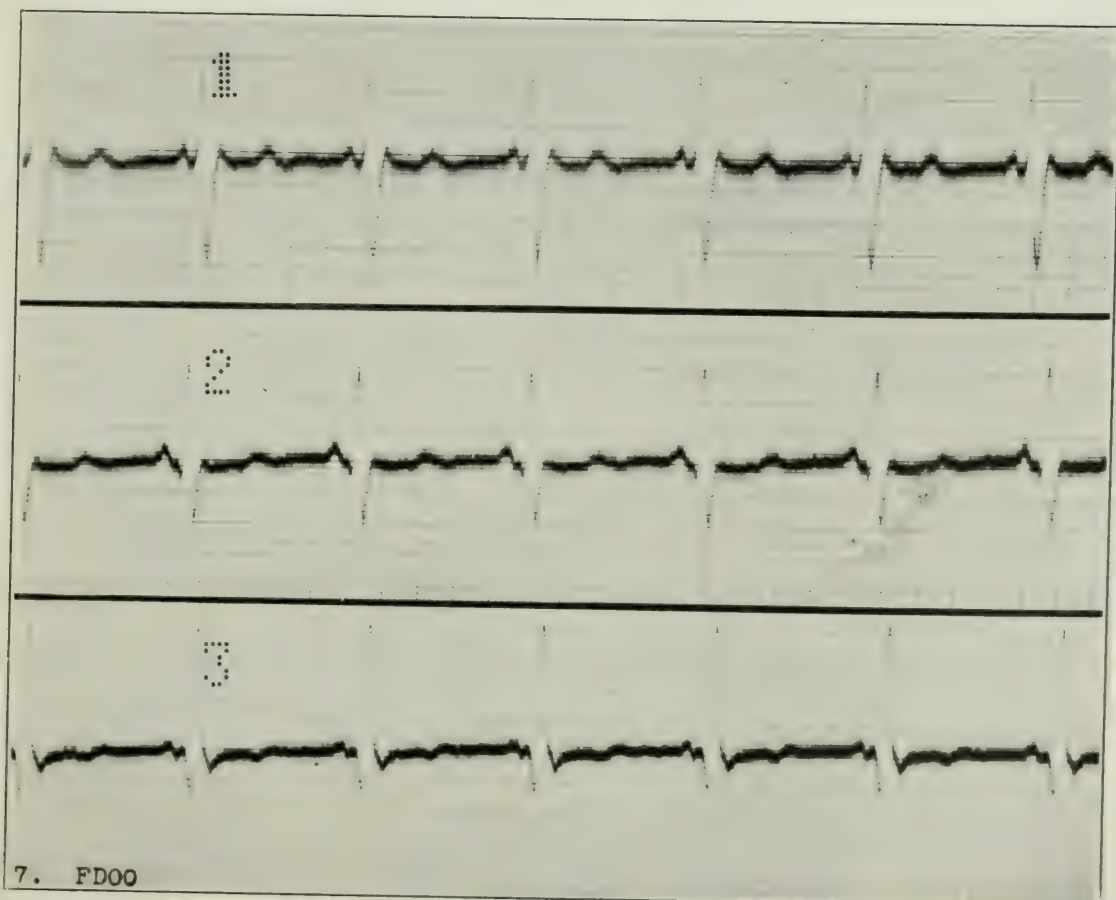


FIG. 7

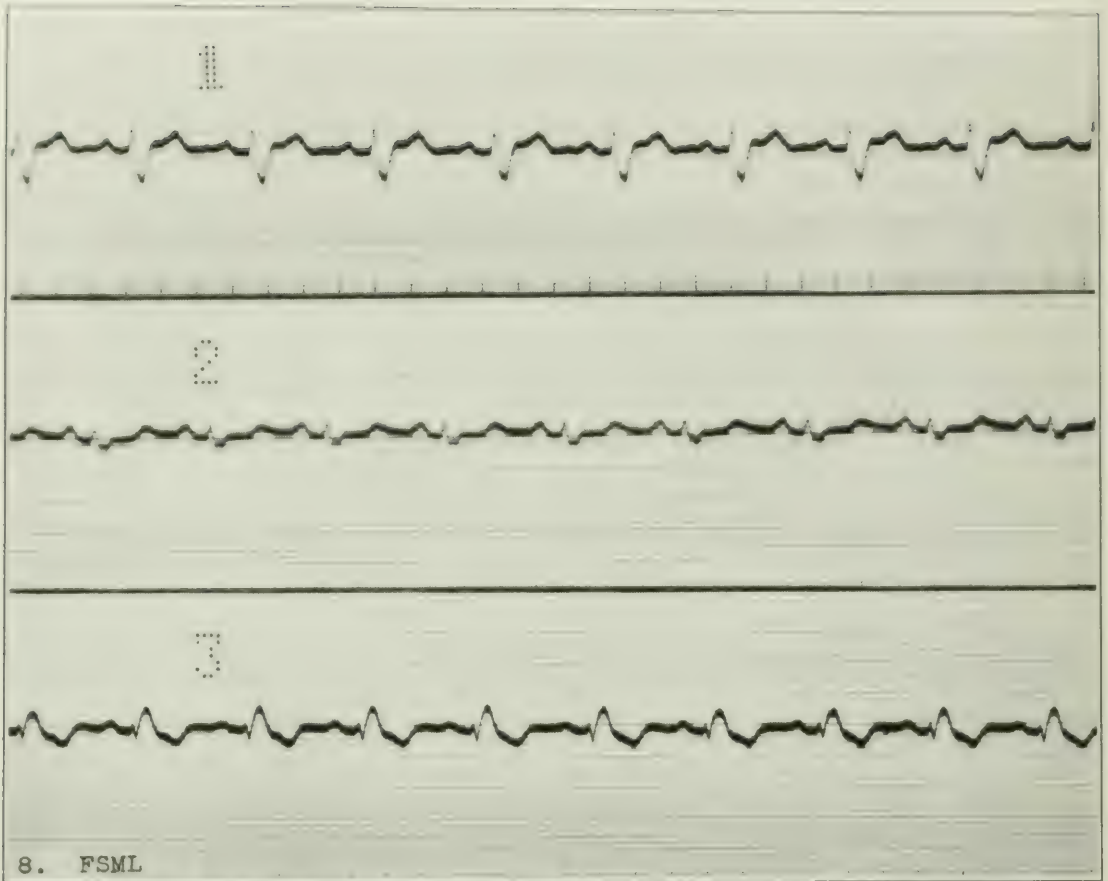


FIG. 8

The clinical picture is about the same in both the groups. Some of the patients had very definite histories of a severe attack of pain, lasting several hours, followed by gradual recovery, while in others the onset did not appear so clearly in the history.

The records of these eight people fall into two groups. In group one the records are like the electrocardiogram of Case *FHHD* and show the typical characteristics that are necessary to diagnose a disease of one bundle branch which completely destroys the function. The R waves or S waves are large and wide and show notches, and the T waves are large and downward in Lead I.

The four remaining records are as in Case *FOPS* and are not so typical of this condition, but they all show marked abnormality in the notching or in the width of the R waves so that the lesion must be considered a serious one, if not complete.

Synopsis of Findings of Eight Additional Examples of Bundle Branch Lesions

Case	Age	Sex	Probable Duration of Disease	Onset	Pain	Dyspnea	Palpitation	Cough	Edema	Rhythm	Blood Pressure	Valves	Murmurs	Response to Digitalis	Size of Heart	Diagnosis	Electrocardiogram
<i>FHHD</i>	76	Male	10 months	Pain on exertion	Yes	Yes	Yes	No	No	Irregular	90-180	Moderately atheromatous	Systolic	Good	Moderately enlarged	Arteriosclerosis	Typical
<i>SHB</i>	48	Male	4 years	Pain referred to epigastrium Pain and discomfort	Vise-like feeling Yes	Moderate on exertion On exertion	Yes	At times	Very slight	Normal	160-220 120-140	Atheromatous Mitral disease	Systolic	Fair	Enlarged	Arteriosclerosis	Typical
<i>FBB</i>	64	Male	3 years				Yes	No	No	Irregular	110-160		Systolic	Using straphantus habitually Good	Enlarged	Advanced Cardiorrenal disease	Typical
<i>FHP</i>	58	Male	2 years	Dyspnea on exertion	Yes	On exertion	None	Very slight	Yes	Irregular	170-200	Normal	None	Good	Large	Arteriosclerosis	Typical
<i>FOPS</i>	61	Female	3 months	Pain on exertion	Yes	On exertion	Yes	No	No	Attacks of fibrillation Regular	Systolic 80-190	Competent	None	Good	Slightly enlarged	Cardiosclerosis hypertrophy	Not typical
<i>FOS</i>	59	Male	6 months	Pain and discomfort	Yes	On exertion	None	None	No	Regular	100-140	Competent	Systolic	Not given	Not enlarged	Arteriosclerosis	Not typical
<i>FD00</i>	81	Male	8 days	Sudden dyspnea and pain	Yes	On exertion	None	None	Yes	Irregular	100-150	Mitral incompetence	Systolic	Good	Slightly enlarged	Senile arteriosclerosis	Not typical
<i>FSML</i>	63	Male	1 year	Palpitation	Nervous feeling	On exertion	Yes	No	No	Regular	100-150	Normal	Systolic	Not observed	Enlarged	Arteriosclerosis	Not typical

The four patients with typical records complained of severe pain over the heart and all showed a greatly increased blood pressure. In the other four there was no increase in blood pressure of any extent, and there was pain in only one person of this group.

The orthodiagrams of the hearts of the individuals with typical records revealed markedly enlarged hearts of the aortic type. Only two of the patients with less typical histories showed this enlargement, the other two having enlarged hearts of the vertical type.

There was only one patient under fifty years of age in this series, he being forty-eight. All the cases were males excepting one. There was no uniformity in the duration of the disease, one man having a normal tracing two and one half years prior to the appearance of a typical bundle branch lesion. Dyspnea and precordial pain were present in all eight people, the precordial pain being most marked in those who had definite bundle branch tracings. These attacks, which were intermittent, came on usually by exertion. In one person it was the chief complaint which brought him for examination. Only two of the typical bundle branch cases were bothered with cough which no doubt was brought on by some congestion in the lungs. The heart valves were not primarily involved in one half of the patients.

Discussion:

DR. PAPPENHEIMER: I would like to ask if these cases were the result of coronary sclerosis or rheumatic myocarditis.

DR. BISHOP: They were almost all the result of coronary sclerosis.

A. D. Hirshfelder gives a very good description of coronary sclerosis in his book on "Diseases of the Heart and Aorta," as follows:

"While the sclerosis of the coronary arteries does not differ in its pathology from the sclerosis of arteries elsewhere, nevertheless the action upon the heart gives rise to clinical and to secondary pathological conditions which are quite different from those of general arteriosclerosis, and which therefore deserve special consideration.

"Another important condition which is very common is arteriosclerotic or atheromatous change arising in the aorta with or without associated involvement of the coronaries themselves, but spreading so as to involve the mouths of the coronaries as they arise from the aorta, and strangulating these vessels as they pass through the aortic wall. This has the same effect as a

metal band constricting an artery would have; namely, of diminishing the blood pressure and the velocity of flow in the artery beyond it, of allowing the walls of the artery to contract down and hence of producing a further permanent secondary narrowing of the lumen, with progressive diminution of the blood supply to the part (Halsted). The course of the artery may show patches of hardening with indentations and widenings, collar-like constrictions or uniform widenings; or on the other hand, the arteries may be converted into uniform tubes whose walls may give the sensation of rubber tubes on the one hand (uniform fibrous sclerosis), or of absolute pipe-stems (complete calcification) on the other. This condition is, of course, particularly common in arteriosclerosis affecting the base of the aorta, *i.e.*, luetic aortitis and luetic aortic insufficiency, and may account for many other symptoms.

"Since the heart muscle requires much more blood when it is beating forcibly and rapidly than when it is beating slowly and quietly, it is easily seen that this collateral circulation may be sometimes adequate and sometimes not. Also, since in different individuals of the same species there are variations both in the structure and disposition of the minute arteries and in the needs of the muscle fibers for nourishment, it is but natural that the results of coronary disease should vary greatly."

109 EAST 61ST STREET

CONGENITAL STENOSIS OF THE DUODENUM ASSOCIATED WITH DEXTROVERSION OF THE AORTA

LUIGI CELANO, M.D.

The uncommon association of cardiac and intestinal congenital malformations seems to me sufficient apology for the report of this case.

The patient was born of a healthy woman of 33, who had had one child seven years before and no miscarriages and who had been operated for retroflexion of the uterus three years before. The pregnancy was uneventful, except for a slight degree of cyanosis.

Parturition was precipitate. The child, a puny female of five and one half pounds, was reported as normal by the interne, but probably was not examined, at the time of delivery. She nursed well in the first three days. On the night of the third day, the infant developed a temperature of 105° F. ascribed by the internes to starvation. The child was given castor oil and had a dark bowel movement in the morning and the temperature dropped to 100. On the fourth day, the temperature went down in the morning and up again in the afternoon and the child vomited. A careful examination was then made. The child looked ill. She was not cyanotic, breathed not too rapidly, 30 to 35 respirations a minute; the abdomen was markedly distended, bulging mostly

in the epigastrium. No visible contractions were noted. The cord was sloughing and pus was oozing from the umbilicus around the stump. On auscultation there was a loud systolic murmur heard over the whole precordium. The murmur was harsh and prolonged. The lungs were clear. Antiseptic treatment was given the cord which the next day looked much better, but some nodules were thought to be felt along the umbilical vessels going up to the liver. On that day (the sixth) the child vomited a few times but not forcibly.

The bowels moved again after enema and some yellow material was expelled suggesting that milk had been digested and passed down the gut. There was never the slightest suggestion of jaundice or cyanosis. Obstruction and congenital heart disease were thought of, but all things put together pointed more to infection of the cord with complicating peritonitis, septicemia and endocarditis.

On the seventh day the child died.

At autopsy the stump of the cord appeared necrotic and oozing pus, but without inflammation around it. On opening the abdomen the peritoneum was

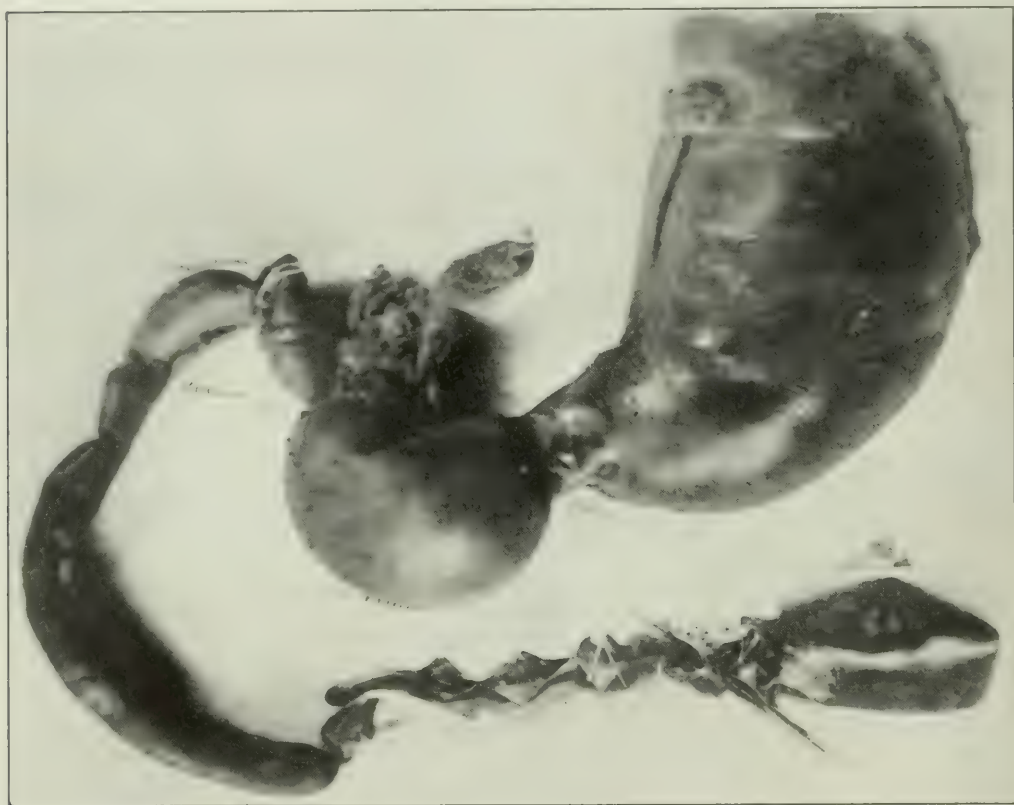


FIG. 1

perfectly normal and so were the umbilical vessels, and the liver. The diaphragm was at the fifth rib on the right side, at the fourth interspace on the

left. The thoracic organs were all normal except the heart. This organ weighed 26 grams. The outside appearance was normal. On opening the right side the right auricle presented a fenestrated membrane at the place of the foramen ovale. There were several punctate perforations and an opening about 3 mm. in diameter, at the lower end. The tricuspid valve appeared normal, and the auricular ventricular ring was 5.5 cm. in circumference, but behind the left cusp the lumen of the ventricle was continued into the aorta. The walls of the conus arteriosus were thick and its lumen very small. The pulmonary orifice was 1 cm. in circumference and the valves white in color and somewhat thickened. The aortic orifice was 24 mm. in circumference and the aortic valves normal. On opening the left heart the auriculo-ventricular ring was 3 cm. in circumference and the mitral valves normal. Behind the anterior valve the lumen of the ventricle was continued into the aorta. The membranous part of the interventricular septum was absent. In the lumen of the pulmonary artery, right back of the bifurcation, there was a minute dimple. No other trace of the ductus arteriosus could be found. The stomach and about the first two and one half inches of the duodenum were enormously distended. The pylorus was perfectly evident but also distended. Right at the entrance of the common bile duct there appeared to be a constriction and all the rest of the intestine below it, small and large, was completely collapsed. On exerting pressure on the stomach or on the distended part of the duodenum, some of the contents could be squeezed into the intestine below the constriction. The head of the pancreas rested around the posterior part of the constriction. On opening the stomach the contents seemed to be practically all milk and there was no bile mixed with it. The intestinal contents below the constriction resembled ordinary meconium.

Close to the entrance of the common bile duct a diaphragm-like occlusion was present.

The circumference of the duodenum above the occlusion was 6 cm. The circumference of the pylorus was 3.5 cm. The circumference of the duodenum below occlusion was 2.5 cm. The surface of the diaphragm-like occlusion toward the stomach a little to the left of the center showed a round depression 8 mm. in diameter, devoid of mucosa, and leading obliquely downwards and to the right in a sinus-like channel which appeared on the distal surface in a slit-like opening, about 1 cm. in length. A small probe could be easily passed through the opening. The pancreas was closely adherent to the posterior surface and each side of the duodenum, at the same level of the occlusion. On the anterior surface at the same level there seemed to be a thickening of the wall. The condition looked similar to an invagination of the mucous membrane by means of a constricting ring-like band. The walls of the duodenum and stomach were extremely thinned out and the folds of the mucosa stretched and flattened. The common bile duct seemed to run with its lower end right through the pancreas and empty within the sinus, in the occlusion.

The heart resembled the typical condition of pulmonary steno-

sis with dextroversion of the aorta and incomplete interventricular septum.

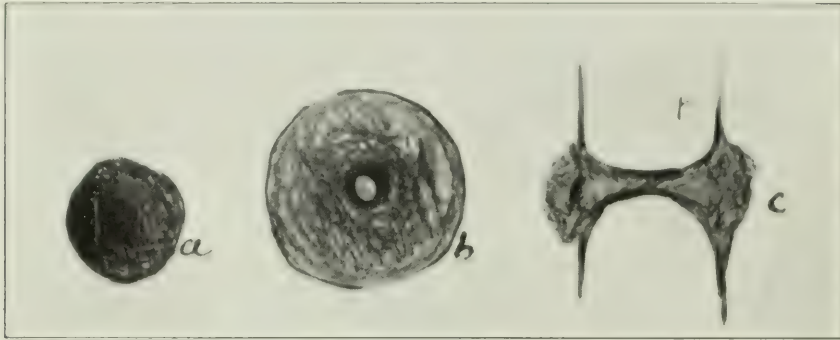


FIG. 2. Diagram of stenosis. *a*, Distal view; *b*, proximal view; *c*, longitudinal section; *r*, connecting tract.

Two explanations can be offered in such cases: (1) Developmental. (2) Inflammatory.

In the developmental explanation it is assumed that the aortic septum for unknown reasons fails to come down and meet the interventricular septum and also divides unequally the truncus arteriosus, thereby leaving a stenosed pulmonary orifice and a communication of both ventricles with the aorta.

In the other explanation an inflammation is assumed causing stenosis of the pulmonary artery before the eighth week of development, that is, before the formation of the interventricular septum. In that way the blood in the right ventricle, finding difficult exit through the pulmonary artery, causes increased pressure in the right ventricle, thereby pushing the septum to the left and bringing the lumen of the right ventricle under the aorta where it finds a freer outlet.

The appearance of the endocardium and the pulmonary valves rather favors the second explanation.

The etiology of the congenital obstruction is still more obscure.

It occurs among newborn children once in 20,000 to once in 50,000 times.

Davis and Poynter in a collection of 431 cases showed the following distributions:

Duodenum	134
Jejunum	60
Ileum and Cecum	101
Colon	39
Multiple	67

In reviewing the literature, almost every author gives a different explanation, but here too two main factors must be considered: (1) Disturbed development. (2) Inflammation.

In the first factor the main point to be considered is the failure of recanalization of the intestinal tube after the period of hyperplasia of the mucous membrane. Another point in connection with development is the possibility of accidents during the growth of the canal. Fetal inflammations when demonstrable give the easiest explanation.

In my case the condition would point more to a kind of developmental accident.

Microscopical sections taken through the long axis of the duodenum and through the occlusion show the occlusion like a shelf protruding within the lumen of the gut. The mucous membrane from each side of the duodenum

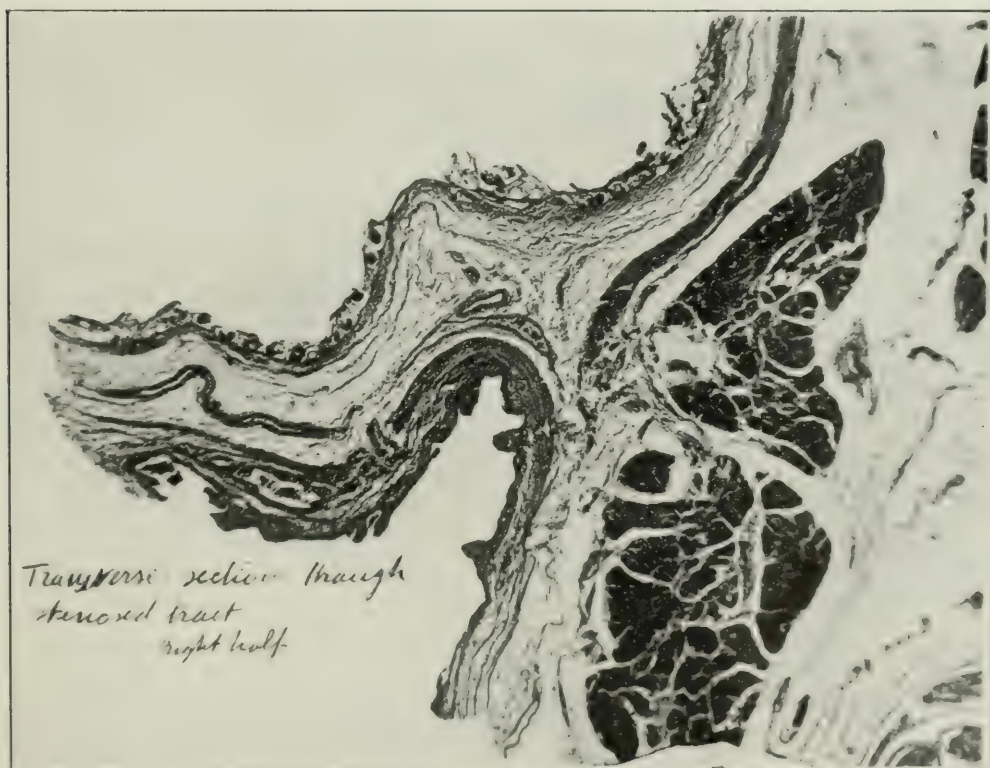


FIG. 3

is continuous on the corresponding side over the shelf. The shelf itself between the two layers of mucous membrane consists of connective tissue containing tubule-like structures resembling pancreatic or bile ducts, and many relatively large blood vessels. A few broken up muscle fibres were also present. The pancreatic tissue is close to the side but not within the tissues of the occlusion. The mucous membrane on the upper surface contains glandular elements similar to those of the duodenum. That of the lower surface is more papillary in form and more similar to the mucous membrane of the jejunum.

Considering the position and structure of the occlusion with the presence of duct elements in it, one is justified in suspecting that the formation of the pancreas may have had something to do with the production of the constriction.

The pancreas develops from at least two outgrowths from the duodenum, a dorsal and a ventral, the last one being connected with the bud of the common bile duct. Some authors sustain that there are up to four outgrowths. It is not hard to figure out that during the process of fusion of those embryonic parts of the pancreas coming out from different points on the circumference of the gut, the organ may undergo torsion on its long axis, or its walls may be held in at some point, while the distal and proximal parts of the organ grow and enlarge freely, and a condition similar to the one found in my case may be produced.

Discussion:

DR. FRASER: I have seen the sections of Dr. Celano's case and I think that the histological picture suggests that the constriction may have been brought about by pulling and twisting of the gut wall by means of the outgrowth and later convergence of the two pancreatic ducts. The lesion, as was seen in the lantern slide, is really an invagination of the wall as if by a constricting band, on each side of which is a pancreatic duct. Now it is not difficult to imagine how these ducts originating at different points in the circumference could in the process of their outward growth and effort to get together produce such an invagination of the portion of the wall lying between them in some such way as that suggested by Dr. Celano in his first explanation. The other suggestion, that the constriction is due to failure of complete canalization of the mucosa of the once more or less solid duodenal tube, does not seem to fit the picture here presented. In such a case we should expect an abnormally thickened mucosa by epithelial hyperplasia or fibrosis, whereas the different layers of the wall are normal and all invaginated together.

DR. MACNEAL: I think constrictions of this sort, though perhaps less rare at the particular site mentioned, also occur in other parts of the gut, and the

explanation of these other obstructions is, it seems to me, extremely difficult on the basis of a pancreatic diverticulum. We recently saw an obstruction in an infant three weeks old who never had done well and who came to the Hospital for intestinal obstruction. The surgeon operated on the case and made a diagnosis of tumor at the lower end of the ileum, and all he did was to connect the ileum to the ascending colon. The child died, and the specimen showed an enormous thickening of the wall at the lower end of the ileum for three cm., and there seemed to be a small cyst or diverticulum into the wall. The mucous membrane was almost completely disintegrated. It might have been something similar to this case. We were unable to decide what caused the condition. The surgeon thought it was a tumor growth but the microscopic examination showed only inflammatory changes, coupled with hypertrophy of the muscular coat. There was evidently obstruction which had proceeded from some maldevelopment. I am inclined to think that these may occur as anomalies in other parts of the intestine. Possibly the region of the papilla of Vater and the ileo-cecal junction may be particularly predisposed to such congenital stenosis.

TETRACHROME BLOOD STAIN: AN ECONOMICAL AND SATISFACTORY IMITATION OF LEISHMAN'S STAIN

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Since Leishman,¹ in 1901, modified Jenner's blood stain by substituting for methylene blue a methylene blue which had been partly decomposed by treatment with dilute alkali and heat (Nocht's polychrome methylene blue), there have been numerous imitations and slight modifications of this stain described by various workers. In this country the best known of these is the modification of Wright.² The results obtained in actual staining by the use of these various modifications are, as a rule, inferior to the pictures obtained by the original stain of Leishman.

In 1905 and 1906³ it was shown that the essential dyes of the Romanowsky stain, of which the Leishman stain is a special application, are four in number, rather than three as had been previously maintained by Giemsa.⁴ These four dyes are eosin, methylene blue, methylene azure and methylene violet. The two

last mentioned substances were first prepared and named by Bernthsen⁵ in 1885. Either methylene azure or methylene violet, in combination with methylene blue and eosin, will produce the red nuclear tint characteristic of the Romanowsky stain. However, the most brilliant and satisfactory results in the staining of blood are obtained when all four dyes are utilized.

Water-soluble yellowish eosin and medicinally pure methylene blue are easily obtainable and are not expensive. Methylene azure, which is now made in the United States by oxidizing methylene blue with chromic acid and heat, is also easily obtainable at a price of 40 to 50 cents a gram, although the German product, Giemsa's Azur I, used to cost five times that amount. A satisfactory preparation of Bernthsen's methylene violet is more difficult to get and it is not listed by the ordinary dealers in dyes. The preparation of an impure methylene violet is not difficult, but its purification by recrystallization from alcohol is difficult and time-consuming. Fortunately the impure, crude substance gives good practical results in staining of blood films.

Crude methylene violet is prepared by dissolving 20 grams of medicinally pure methylene blue in nine liters of water and then adding 20 grams of crystalline sodium carbonate, previously dissolved in one liter of water. The mixture is then heated to boiling for five to ten hours. The precipitate of long needle crystals is filtered out, washed with distilled water, and dried on a porous plate. The yield is about 5 grams (25 per cent.). This substance is crude methylene violet. The chief impurities are methylene blue and methylene azure and lesser amounts of difficultly soluble, unidentified substances. These impurities do not seriously impair the usefulness of the product.

In collaboration with Schule,⁶ in 1913, it was determined that a mixture of the following composition gave most excellent results in the staining of blood cells and hematozoa.

Water-soluble eosin	1.0 gram
Medicinally pure methylene blue	1.0
Methylene azure, recrystallized	0.6
Methylene violet, recrystallized	0.2
Pure methyl alcohol (Merck's Reagent).....	1000.0 c.c.

At that time we recommended the preparation of the stain in two solutions, keeping the eosin separate from the other three dyes, and mixing the two solutions in equal parts shortly before use. The separate solutions keep well for two years, but not for four years. The deterioration appears to be due to the slow oxidation of the alcohol. This change is more rapid when the four dyes are present in the same solution. For the last nine years these solutions have been employed in the routine staining of blood films at the Post-Graduate Laboratories, crude products of methylene violet being substituted for the highly purified sample employed in the original tests.

Since 1919 an attempt has been made to interest American dye chemists in the manufacture of methylene violet and particularly in the preparation of a finely ground mixture of the four dyes in a dry state, ready to be dissolved in methyl alcohol in the proportion of 3 grams to a liter of alcohol. For this mixture of the four dyes the name Tetrachrome Blood Stain has been suggested. Crude methylene violet is used in double the quantity indicated for the pure substance in the above formula.

One manufacturer¹ has prepared a satisfactory mixture of this sort which is designated as tetrachrome blood stain and priced temporarily at one dollar for ten grams, enough for more than three liters of staining solution. An effort is now being made to interest other manufacturers and dealers.

This stain is recommended as a satisfactory imitation of the Leishman stain because of the excellent results in staining blood films, the uniformity of composition and the low cost. The latter is of some importance in large hospitals where many specimens have to be examined daily.

References

1. LEISHMAN: *Brit. Med. Jour.*, 1901, ii, 757.
2. WRIGHT: *Jour. Med. Research*, 1902, vii, 138.
3. MACNEAL: *Jour. Inf. Dis.*, 1906, iii, 412.
4. GIEMSA: *Centralbl. f. Bakt.*, 1902, xxxi, 429.

¹ Calco Chemical Company, 136 Liberty Street, New York.

The National Aniline and Chemical Company, 21 Burling Slip, New York, has recently prepared this stain also.

5. BERNHUSEN: *Liebig's Annal d. Chemie*, 1885, CCXXX, 137.

6. MACNEAL AND SCHULE: *The Post-Graduate*, 1913, XXVII, 982.

Discussion:

DR. EWING: I think Dr. MacNeal has done a distinct service in bringing this before us. Does it stain spirocheta well? Have you tried it on tissues?

DR. MACNEAL: Yes. I haven't done anything with tissues; perhaps it would work out, but I haven't tried it.

BLOOD CHANGES IN MYELOGENOUS LEUKEMIA FOLLOWING RADIUM TREATMENT

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Dom Etienne Gilbert in the Paris *Theses* of 1914 describes a number of cases of myelogenous leukemia treated by radium, in which excellent results took place, the red cells increasing to their normal level and the leucocytes decreasing to nearly their normal level with general improvement of the patient's health. But ordinarily, the cure, according to Gilbert, is not stable, the signs of leukemia often reappearing after some weeks have passed, and with radium treatment the number of leucocytes diminishes less rapidly, the curative action of radium very likely being weakened.

G. Lovell Gulland in the *British Medical Journal* of August 30, 1921, describes the treatment of myelogenous leukemia with radium, and while he cannot say the benefit has been permanent, it has been certain and more rapid than that of x-ray. The first obvious effect has been a reduction of the leucocyte count, the neutrophiles, both the polymorphonuclear and myelocytic forms being most affected in this decrease. Next are the eosinophiles and basophiles while the lymphocytes and mononuclears are less affected. The nucleated red cells practically disappear, and in successful cases the blood may return to a nearly normal appearance. The spleen grows smaller although it never goes back to its actual normal size, for with its increased fibrosis one would scarcely expect it to do so.

Dr. James Metcalf in the same journal regards radium as of excellent value in leukemias, especially the myelogenous form, and mentions the case of a man of fifty-nine, afflicted with the latter, who showed marked improvement from radium treatment. The radium was applied over the spleen, sternum, and epiphyses of the femora and humeri. He believes that the doses must be massive and frequent as small doses only stimulate the abnormal conditions.

Within the past two years at the Post-Graduate Hospital studies have been made of the blood changes in myelogenous leukemia following radium treatment as will be seen in the following case.

CASE I. William E. —, aged 14. He first came to the Post-Graduate on April 27, 1920, with the following clinical picture.

His family and previous history were negative.

In July, 1919, his mother noticed that he did not play with his former vigor and energy, and that he was pale and complained of weakness and loss of appetite. He was examined and given medicine by a physician and continued to decline in health. In October he was sent to the Staten Island Hospital for an enlarged spleen; he remained there for a month, but was afterwards discharged with a bad prognosis.

Physical examination showed the patient to be thin and generally anemic in appearance. The lungs and heart were negative except for a soft systolic murmur of the latter at the second interspace. The abdomen was protuberant and distended by a large mass on left side, firm in consistency, extending obliquely downwards from the left hypochondrium to within 25 cm. of the pubic symphysis. The liver was palpable 8 cm. below the costal margin. No free fluid was made out. The superficial veins were prominent over the entire body, especially over the abdomen and lower extremities.

The Wassermann test, taken April 27, was negative.

Provisional diagnosis: Splenomyelogenous leukemia.

On April 28, the first blood count was taken which showed 3,150,000 red cells per cubic mm. and 164,800 leukocytes and 50 per cent. of hemoglobin. A differential count of 500 white cells showed 35 per cent. of polymorphonuclear neutrophils, 36 per cent. of lymphocytes, mononuclears and transitionals, 7.2 per cent. of eosinophiles, 7.6 per cent. of basophiles, 37 per cent. of neutrophilic myelocytes, 7.4 per cent. of eosinophilic myelocytes, 3.2 per cent. of basophilic myelocytes and 4 per cent. of myeloblasts. A few normoblasts and macroblasts were seen among the red cells. Some more smears were taken two days later which showed a similar blood picture, with an occasional myelocyte undergoing mitosis.

On April 29th, at 4 P.M. 100 mgm. of radium were applied over the region of the enlarged spleen, the dose being changed every hour in fourteen succes-

sive applications. On May 4th the leucocytes had fallen to 135,400, but two days later, the blood count showed a rise in the leucocyte count to 312,000, but another count taken on the following day showed a fall to 202,000.

The second dose of radium was applied on May 10th, when 100 mgm. were applied, beginning at 3:50 P.M., in twelve successive applications.

By May 13th the leucocyte count fell to 199,000; two days later it had fallen to 162,000 and by May 20th it was 77,400.

On the 26th it was found that leucocytes had increased to 118,400 and on this date 120 mgm. of radium were applied over the spleen in eleven successive doses. The leucocyte count began gradually to diminish, going down to 112,000 by June 1st and 111,000 by June 3d. On that date 120 mgm. of radium were applied in seven successive applications of two hours each. On June 7th the leucocytes had diminished to 52,000 while the red cells had increased to 3,926,000. On June 8th the patient was discharged.

On July 2d he returned for examination and treatment. The spleen was now greatly reduced in size, the splenic notch being 9 cm. from the tip of the xiphisternum, the lower border 14 cm. from the ninth costal cartilage and the right border 14 cm. from the median line. The leucocytes had fallen to 12,000. On the sixth 120 mgm. of radium were given at 10 A.M. in four successive applications of two hours each. He returned on Sept. 9th and the leucocytes were found to have increased to 28,400. He was now given 60 mgm. of radium in eight successive applications for sixteen hours. On Oct. 7th when he came again the leucocyte count was the same, but the polynuclear neutrophils had risen from 14.484 to 17.792 and the lymphocytes and mononuclears had risen from 1,420 to 8,400, while the myelocytes had fallen to practically nothing. On Oct. 28th, when he came again for treatment, he showed a decided improvement, the leucocyte count being 15,400 and the blood picture appearing much more normal. The spleen was firm and palpable and the patient had gained ten pounds in weight, his weight now being 79 pounds.

During the winter and spring the patient called at intervals of nearly every month for treatment, and on each visit he was given radium in five successive applications of three hours each. The polymorphonuclear neutrophils approached more nearly their normal level, and the myelocytes showed a marked decrease, none being found in the differential counts taken in February and March, and only a few being found in the count of May and June. The patient's general condition was greatly improved, the anemic pallor and prominence of the superficial veins being gone, and the spleen was reduced to nearly a quarter of its former size.

The patient was away in the country during the summer, but returned for treatment on September 1st. Here it was found that the leucocyte count was 69,800 per c.mm. with an increase of myelocytes above the lymphocytes, so he was given 90 mgm. of radium for eighteen hours in six applications. He returned a week later for treatment and this time the leucocyte count was 20,000. He was given 100 mgm. of radium in four successive doses of four hours each.

On September 29th the patient came to the hospital with weakness, drowsi-

ness, loss of appetite and fever, and a herpetic sore on the lower lip. The leucocytes had risen to 58,200 but the differential count showed a striking contrast in that the polynuclear neutrophiles had fallen to 4 per cent. or only 2,328 while the lymphocytes had risen to 35,596 or 68 per cent. The patient bled occasionally from nose and rectum. The red blood cells were 2,328,000. On October 7th the leucocytes had fallen to 1,800 and the anemia was more marked. The sore on the lower lip had formed an ulcer the size of a silver dollar, and this was diagnosed as gangrenous septic dermatitis following deep infection of the herpetic sore, which the patient was unable to resist on account of the leucopenia. By October 18th the leucocytes were 310, the red cells 1,148,000 and the hemoglobin 23.5 per cent. On October 25th the patient was transfused with 500 c.c. of blood, but improvement was only temporary. On November 1st the red cells were 1,252,000, the hemoglobin 24 per cent., and the leucocytes 380 per c.mm. of which there were 18 per cent. polynuclear neutrophiles, 70 per cent. lymphocytes, and 12 per cent. basophiles. The patient died that night at eleven o'clock.

The autopsy performed the next day at 9 A.M. showed the following:

Gross anatomical findings. Abdomen: Two thousand c.c. of opalescent yellow fluid containing fibrin flakes were in the abdominal cavity.

The spleen was enlarged, weighing 780 grams, adherent to parietal peritoneum beneath cutaneous scars, and contained deep fibrous scar tissue sending fibrous trabeculæ into the splenic substance.

The liver weighed 1,930 gm., the capsule was thickened and lobules enlarged.

The posterior mesenteric vein and tributaries were congested. The mesenteric and retroperitoneal lymph nodes were brown and moderately enlarged.

There was gelatinous edema of the retroperitoneal tissue behind the ascending colon with gas bubbles and putrefactive odor, evidently due to agonal invasion of anærobic bacteria.

Thorax: There was two hundred c.c. of clear yellow fluid in each pleural cavity.

Posterior portions of both lungs showed edema, with a firm airless reddish-brown nodule in the upper lobe of the right lung.

Small petechial hæmorrhages were in the parietal layer of the heart and beneath the pericardium. The heart muscle was pale.

The yellow marrow of the long bones was replaced by dark red marrow.

Microscopic Findings: Spleen: The capsule showed dense fibrous thickening with thick fibrous scar tissue extending into the splenic substance by irregular fibrous trabeculæ, infiltrated along the borders with hemosiderin granules. The Malpighian corpuscles were largely replaced by fibrous connective tissue and the splenic pulp was infiltrated by a fibrous network with many sinuses and capillaries. Only a few small patches of round cells resembling splenic pulp, and occasional accumulations of red cells were found; many round cells, few polynuclear and eosinophile cells and very few myelocytes were found. The red cells in the vessels were very scanty and there was evidence of hemolysis.

Bone marrow: Smears from the marrow of the third lumbar vertebra showed out of a count of 200 cells, 12 polynuclear neutrophiles, 112 lymphocytes and mononuclears, eosinophile, 4 basophiles, 26 neutrophilic myelocytes and 33 disintegrated cells. Occasional nucleated red cells were seen. In the section the marrow consisted of ragged masses of red corpuscles, including many normoblasts with occasional macroblasts and few megaloblasts and rarely a giantoblast. Neutrophilic and eosinophilic myelocytes and occasional polynuclear cells were seen, with large numbers of nongranular mononuclear cells greatly outnumbering the myelocytes and the polynuclears.

Smears from the shaft of the femur showed out of a count of 200 cells, 8 polynuclear neutrophiles, 114 lymphocytes, 6 eosinophiles, 3 basophiles, 12 neutrophilic myelocytes, 3 eosinophilic myelocytes, 1 basophilic myelocyte and 33 disintegrated cells. During the count 19 normoblasts, 7 microblasts, 4 macroblasts and 1 megaloblast were found. In the sections the marrow substance showed a more compact mass of cells than in the third lumbar vertebra. The myelocytes and polynuclears were more abundant and large numbers of nongranular mononuclear cells were seen. Sections from a rib and from the sternum showed a similar appearance to that of the third lumbar vertebra, except that the myelocytes and polynuclears were more scanty.

Liver: Some of the cells contained minute fat particles brought out by Scharlach R. stain. In a few places hemosiderin granules were found in the intercellular channels. In one area these channels were distended into spaces resembling alveoli, from 1/40 to 1/10 mm. in size, evidently having formerly been distended with accumulations of myelocytes.

In the mesenteric lymph nodes the lymphoid tissue was mingled with red cells, largely disintegrated. In some glands there was an increase of fibrous connective tissue in and around the lymphoid tissue with some thickening of the vessel walls.

Lungs: In a section including the nodular portion, the alveoli were solidly filled with blood, but some contained plasma with few red cells, many of these being disintegrated. The alveolar capillaries were much engorged. Very few leucocytes were found, except endothelial cells, of which there were many.

In conclusion it will be seen that while the patient was being greatly benefitted for the time by the radium treatment, its effects were temporary and when the patient discontinued treatment for two months, he suffered a relapse. His subsequent condition showed the need of using the utmost caution in giving radium treatment, especially after a relapse, because then the resistance is so apt to be lowered. While the first dose of radium after the patient's return did bring on an apparent improvement in the blood picture, the most striking phenomenon after the second dose was the rapid fall in polynuclear leucocytes, the blood picture almost resembling lymphatic leukemia, and the rapid

leucopenia and anemia which followed, resulting in the patient's death.

Discussion:

DR. MOSCHCOWITZ: I have no experience in treating leukemia by radium. It seems to me that from the pathology of the disease the application of radium to the spleen alone, or even to a portion of the bone marrow, could hardly affect the malady to any great extent. Certainly Dr. Witcher has obtained some changes in the blood picture by the use of radium to the spleen, but whether the change in the blood picture is an indication of the change in the leukemic process I venture to doubt. We have all seen changes in leukemia by the use of other methods than that of radium. You will recall the striking changes after the use of benzol, but these are entirely temporary, and have no permanent effect on the patient. It seems to me that if radium is to prove beneficial in leukemia it must be applied in a form which will reach every portion of the reticulo-endothelial apparatus.

It was especially interesting to me to note the transformation of the case from a leukemia to a leukanemia. It seems to me that this transformation resulted from an exhaustion of the bone marrow and consequent interference with hematopoiesis. It shows what I have always suspected, that leukanemia was not a disease in itself, but was simply a terminal phase of a leukemia, or perhaps of a pernicious anemia in which a compensatory terminal stimulation of the bone marrow led to the presence of embryonal forms of leucocytes in the blood.

DR. EWING: I think Dr. Moschcowitz's conception of the pathology of the disease forms the only sound basis for any attempts at therapy, either by radium or by any other agent. Since we know the essential lesion is located in the bone marrow, and pretty much in all the bone marrow, we might very well ask what is the use of applying a little radium to a big spleen. However, our theories receive a jolt when we actually witness the transformation of the patient clinically who has received a little radium over an enlarged spleen; the improvement is often quite remarkable, and in some cases it has lasted very much longer than in that reported to-night. Our work at the Memorial Hospital has led us to the conclusion that Dr. Moschcowitz mentions, that unless we have a constitutional agent, we cannot hope to find a cure for the disease. Therefore in several cases we injected a solution of radium deposit into a vein. That would give all the effects of the alpha, beta, and gamma rays. In several cases of leukemia treated in this way there were sharp constitutional reactions, with very pronounced changes in the circulating leucocytes, and a rather long continued improvement in the condition of the patient. I think most of those cases are now dead. They were treated three or four years ago, but I know of one woman who is still living and apparently well. The details of her blood picture I cannot give. However, that method failed notably in a certain case which came to autopsy, for reasons which were perfectly definite. We found the bone marrow everywhere solidly packed with cells like a leukosarcoma. There were large deposits of tumor-like masses in the liver, and the lymph nodes were firm and filled with large cells. Histologi-

cally we called it a leukosarcoma, and of course the local application of radium is not going to cause a regression of a universal leukosarcomatosis. On the other hand, there was such a remarkable, although temporary, change in the clinical picture in this case that it would seem that the local applications do have some peculiar constitutional effect which is very difficult to explain. It has recently been suggested that the best method of regulating dosage is by observation of the total metabolism of the patient as indicated by the urinary nitrogen. When it comes to normal, do not attempt to add to the effect by increasing the dosage. Disregard the leucocyte count, and treat the patient rather than the leucocytosis. I am not prepared to say anything about this method, but Dr. Stone at the Memorial Hospital has come to the conclusion that it is best to treat these cases very cautiously.

DR. MACNEAL: It seems to me that the importance of presenting a case of this sort is to bring out discussion. If anyone understands clearly how radium affects the pathological process, and the exact pathology of leukemia, I should like to learn it, and therefore I feel that discussion is tremendously important. I also feel that reports concerning the results of treatment of leukemia by radium are valuable, especially when the full returns are in, as in this case, and that those cases which were last observed alive after a period of treatment of one or two years are less valuable. I have very grave doubts as to the eradication of the pathological condition by any method of treatment in the case of leukemia. My enthusiasm for publication of the report presented by Dr. Whitcher increased after the patient died, as I regard such a completed case as much more valuable. Concerning the effect which radium has on the disease by the mere local application to the spleen, I think there cannot be very much doubt about it. It really does produce changes in the blood. In regard to the treatment of the long bones by radiation, *x-ray* or radium, I might say that in the early days there was a good deal of enthusiasm in giving larger, strong doses to the long bones as well as to the spleen, and the results were so effective that we did not feel like bringing them before any society; the patients promptly died. One has to be extremely careful about the amount which is applied in these cases. Whether it is wiser to give minute doses over a large area of the body, or rather a severe burn over the spleen is debatable. In the case here reported the patient lived for over a year under observation. He had a vacation and went to the country. Upon his return he was actually not so well, and the attempt to make up for lost time by giving him heavy doses was followed promptly by a very unfavorable change in his condition.

DR. WHITCHER: In regard to applying radium over the long bones, we discontinued that at the Post-Graduate Hospital, because the danger is that it will have a destructive effect on the marrow of the bones, so that it prevents the marrow from producing new red blood cells and hemoglobin, and so does more harm than good. The principle of applying the radium over the spleen is to stimulate the fibrosis in that organ, and so check the growth of myelocytes there, which, where there is no fibrosis, goes on unchecked, the cellular tissue of the spleen not being held under the limitations that the marrow of the bone is, according to Dr. Cabot's theory. He claims that in the spleen

the marrow cells are not held in check as they are in the bone marrow, so the spleen grows larger and larger, unless fibrosis takes place, and where that takes place, it retards the growth of the organ and the patient's life is prolonged; so that evidently the principle of applying radium over the spleen is in the stimulation of fibrosis and its effect on the disease. I think it likely when the patient came back and had the first dose of radium, and the cells dropped to 20,000, that if he had only been given a smaller one or allowed to go without it for the time, his life might have been prolonged, but such a large dose acted as too much, just as a severe pyogenic infection overwhelms the patient, by its overstimulation and toxic effect upon the bone marrow, destroying its ability to produce new cells.

A CASE OF SPINDLE-CELL FIBROBLASTIC SARCOMA OF THE THYROID GLAND

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Sarcoma of the thyroid gland takes on a new interest since Dr. Ewing has said in his "Neoplastic Diseases" under the title "Sarcoma of the Thyroid Gland": "the occurrence of true sarcoma in man still requires demonstration." In any event primary sarcoma of the thyroid gland is of sufficient rarity to justify the presentation of what we believe to be a true spindle-cell sarcoma of the thyroid gland.

Spindle-cell sarcoma of the thyroid, classified according to the morphology of the cells, has been reported about once a year since 1876. Foerster had recorded one in 1860 and Mueller one in 1871, both giving detailed histological descriptions. Luecke in 1875 refers to reports of spindle-cell sarcomas. Doléris and Socin, in 1876, each reported a spindle-cell sarcoma and, in 1879, sarcoma of the thyroid was given important consideration by Kaufmann, who referred to the spindle-cell sarcomas of Mueller and Rose and reported one of his own. Kaufmann's classical description of spindle-cell sarcoma has been the basis of most later microscopical studies. He was one of the first to speak of sarcoma and carcinoma occurring together. He pointed out

that the origin of all sarcomas must be in the interstitial tissue. In 1879 also Rose collected nine sarcomas, one of which was a spindle-cell sarcoma according to the microscopical examination made by Professor Eberth. Heath, also in 1879, reported a spindle-cell sarcoma in which "no trace of the original structure of the thyroid was to be found."

In 1881, Bircher collected sarcomas of the thyroid from the literature and found three spindle-cell sarcomas. In the same year Tillaux reported a spindle-cell sarcoma, giving detailed microscopical description. Wohlfler, in 1883, reported a fibro-sarcoma but in his report he described atypical epithelial proliferation that was of a carcinomatous nature. The same year Koch, speaking for himself and Demme, said sarcoma and carcinoma occurred together and that they could be differentiated only by the microscope and that the differentiation between them was of no practical value. In 1883, also, Braun tabulated the sarcomas of the thyroid from the literature and found spindle-cell sarcomas reported by Czerny, Kaufmann and Sonnenberg. He himself reported one spindle-cell sarcoma. Two years later Rotter collected malignant tumors of the thyroid and added a mixed round-cell and spindle-cell sarcoma. Bowlby in 1885, also, reported a fibro-sarcoma of the thyroid, stating that sections taken from the periphery and the center were entirely fibrous without the least appearance of either alveolation or of epithelial cells. In 1886 Moore reported a spindle-cell sarcoma of the thyroid. The pathological report states that in the portions examined no trace of the original gland tissue was found. The same year Kobler reported a spindle-cell sarcoma with "a partially alveolar structure." In 1887 Shattuck, and in 1888 Ploennis, Jones and Battle reported spindle-cell sarcomas of the thyroid. In 1889 Orcel included two spindle-cell sarcomas in his series of malignant tumors of the thyroid, one of Frerich's and one of his own. In 1891, Roux added a fibro-sarcoma to his list of reported cases. In 1897, Rabé reported a mixed round-cell and spindle-cell sarcoma that Ehrhardt later cites as a spindle-cell sarcoma. The same year Reverdin and Buscarlet reported a spindle-cell sarcoma of the thyroid. In 1897 also, Tiffany and

Lanier collected fifteen sarcomas of the thyroid and of these seven were spindle-cell sarcomas, one of which was their own case. In 1898 Limacher made an exhaustive study of spindle-cell sarcomas and concluded that the tumor cells were related to the blood-vessels in his cases. In the same year Kummer reported a thyroid tumor showing both carcinomatous and typical sarcomatous spindle-cells.

In 1899, Morf collected forty sarcomas of the thyroid, six of which were spindle-cell, three fibro-sarcomas and seven of the mixed-cell type. The same year Ewald reviewed sarcoma of the thyroid and stated that spindle-cell sarcomas do occur. In 1899 also, Schiller reported three spindle-cell sarcomas from the Heidelberg surgical clinic. Firth in England, the same year, reported a tumor of the thyroid that is later referred to by Ehrhardt as a spindle-cell sarcoma. Also in 1899, Cumston reported a spindle-cell sarcoma. Lartigau in 1901 added fifteen sarcomas to the forty collected by Morf three years previously. He stated that spindle-cell, round and mixed-cell tumors are the most common. In 1902 Ehrhardt cited seventeen spindle-cell and seven fibro-sarcomas found in the literature and remarked that fibro-sarcomata are difficult to distinguish from scirrhous carcinoma. In 1904 Papin and Saborianu reported a typical sarcoma made up of spindle-cells, the thyroid tissue represented only by a thin layer of cells pressed against the periphery. Saltykow in 1905 reported a typical spindle-cell sarcoma in the left lobe of the thyroid and a mixture of carcinoma and sarcoma in the right lobe and refers to the similarity of the cases reported by Ehrhardt, Kaufmann, Kummer and Woelfler.

Mueller and Speese in 1906 added eighteen sarcomas to Ehrhardt's list, making a total of one hundred eighteen, of which thirty were spindle-cell or fibro-sarcomas, among them a spindle-cell sarcoma of their own. The description of their tumor closely follows Kaufmann. Kocher in 1907 reported forty-six malignant tumors of the thyroid and made the illuminating statement that all but one of these proved to be of a carcinomatous nature although in some cases the tumor was supposed at first to be a spindle-cell sarcoma until careful examination revealed its epithe-

lial nature. He also described carcinoma and sarcoma occurring together. In the same year Herrenschnidt reported a spindle-cell sarcoma, saying it also showed alveolation suggesting epithelium and nodules of true epithelioma. Also in 1907, Vanderveer reported a fibro-sarcoma. In 1908, Williams reported one case of sarcoma of the thyroid, type cell not given. He is very emphatic in stating that sarcoma and carcinoma occur together but that transitions from one to the other have no existence, Virchow to the contrary, notwithstanding. In 1909 Michel reported spindle-cell sarcoma and carcinoma in the same tumor. Chambers in the same year collected the sarcomas of the thyroid found at the Royal Free Middlesex Hospital in a period of ten years and of these four were spindle-cell sarcomas. The author stated that these sarcomas are similar in structure to sarcomata occurring in other organs. In 1913 Porter added five sarcomas to those previously reported by Mueller and Speese, one a fibro-sarcoma and his own case which was "undoubtedly a spindle-cell sarcoma" according to the pathologist. Also in 1913 Wissmer-Kovarsky, directed by Professor Askanazy, reviewed the reported cases of malignant tumors of the thyroid gland. She noted that histological classifications do not agree, expressing regret that Langhans did not clear up the difficulty. She cited three spindle-cell sarcomas, only one of which had the classical appearance of sarcoma without a trace of epithelial cells. She indicated her skepticism by propounding the question, "Is there such a thing as sarco-carcinoma?"

In 1917 Crotti reviewed the literature in preparation for a paper on malignant goitre and made the statement that a differential diagnosis between carcinoma and sarcoma is evidently not easy. His observations were chiefly clinical. In 1917 also, Vandenberg described a case of spindle-cell sarcoma of the thyroid. The microscopical description was by Professor Warthin. Binnie in 1918 complained that the histological description of malignant tumors of the thyroid is most confusing. He reported a spindle-cell sarcoma. The histological examination was made by Professor Welch. In 1919 Kreglinger reported one case from the Hanover Hospital which he designated as a typical spindle-

cell sarcoma. In the same year Simpson reported the malignant tumors of the thyroid found in the New York State Hospital at Buffalo and stated that the sarcomas are usually of the spindle-cell variety. Von Rijssl in 1920 reported a mixed round-cell and spindle-cell sarcoma. Also in 1920, Bouman reviewed the literature and found one hundred eighty carcinomas to one hundred ten sarcomas. He made no attempt to classify them except clinically. However, he did mention fibro-sarcoma. It is noticeable that the authors of the significant reviews in American literature give little attention to the histology of sarcoma of the thyroid.

In 1920, Berry reported two sarcomas of the thyroid without microscopic description. In 1907 he had reported a spindle-cell sarcoma and in 1901 three spindle-cell sarcomas, one of which was his own case. This case was cited by Ehrhardt in 1902.

In 1921 Wilson reviewed the literature of malignant tumors of the thyroid, reported since 1914, and discussed the sarcomas observed at the Mayo Clinic together with those reported to him by personal correspondence from sixty-seven American surgeons. According to Wilson's view, spindle-cell sarcoma is the most common type of sarcoma of the thyroid gland and such tumors almost invariably contain large or small groups of parenchymatous (epithelial) cells which are also proliferating. He has reported nineteen sarcomas, ten of which are classified, including among them tumors designated as carcino-sarcoma, adeno-sarcoma and one spindle-cell sarcoma. He has stated that we must continue to call these tumors sarcomas whatever may be our hypothesis with regard to their epithelial or mixed origin.

Speese and Brown, in 1921 also, reported nineteen carcinomas and three sarcomas of the thyroid, without classifying the latter. In this report they mentioned the occurrence of carcinoma with sarcoma.

In Table 1 is shown the chronological list of reports of carcinoma, sarcoma and spindle-cell sarcoma.

The earlier reports are unconvincing. It would appear, however, that there are reports of six fibroblastic sarcomata which

cannot be thus dismissed, namely, those reported by Heath, Tillaux, Bowlby, Moore, Porter and Kreglinger, while those by Vandenberg and Binnie seem to be authentic.

TABLE 1

Malignant Tumors of the Thyroid Gland

Reported by various authors, classed as carcinoma and sarcoma and as spindle-cell sarcoma

Year	Author	Carcinoma	Sarcoma	
			Total	Spindle-cell
1866 . . .	Foerster	4	3	1
1871 . . .	Muller		1	1
1876 . . .	Doleris		1	1
1876 . . .	Socin		1	1
1879 . . .	Rose	9	4	1
1879 . . .	Kaufmann (lit.)	12	3	2
	Kaufmann (own)	11	3	1
1879 . . .	Heath		1	1
1880 . . .	Maas		1	1
1881 . . .	Bircher		8	3
1881 . . .	Tillaux		1	1
1883 . . .	Wolfier		5	1
1883 . . .	Braun (lit.)	51	12	2
	Braun (own)	3	4	1
1885 . . .	Rotter (lit.)	13	3	?
	Rotter (own)	5	1	1
1886 . . .	Bowlby		1	1
1886 . . .	Moore		1	1
1886 . . .	Kobler		1	1
1887 . . .	Shattuck		1	1
1889 . . .	Orcel	11	5	3
1891 . . .	Roux	3	4	1
1892 . . .	Pick		1	1
1897 . . .	Rabé		1	1
1897 . . .	Reverdin & Buscarlet		1	1
1897 . . .	Tiffany & Lanier		15	7
1898 . . .	Limacher	38	44	?
1898 . . .	Kummer		1	1
1899 . . .	Mori		40	6
1899 . . .	Ewald	?	?	?
1899 . . .	Schiller	3	23	3
1899 . . .	Firth		1	1
1899 . . .	Cumston		1	1
1901 . . .	Lartigau		15	?

As another addition to this list, the following case is presented:

The patient, Lydia Magnarello, a girl of sixteen years, was admitted to the New York Post-Graduate Hospital, February 25, 1921, service of Dr.

Moorhead. The family history was negative, and the patient had always been a healthy girl except for the present illness.

TABLE I (Continued)

Malignant Tumors of the Thyroid Gland

Reported by various authors, classed as carcinoma and sarcoma and as spindle-cell sarcoma

Year	Author	Carcinoma	Sarcoma	
			Total	Spindle-cell
1901.....	Carrell	80	3	?
1901.....	Berry	13	20	1
1902.....	Ehrhardt	150	99	17
1904.....	Papin & Sabareanu		1	1
1905.....	Saltykow		1	1(?)
1906.....	Muller & Speese	181	188	30
1907.....	Langhans	?	1	1(?)
1907.....	Kocher	44	1	1
1907.....	Herrenschmidt		1	1
1907.....	Berry	5	2	1
1907.....	Vanderveer		1	1
1909.....	Michel		1	1
1909.....	Chambers	15	8	4
1913.....	Porter		5	1
1913.....	Wissmer-Kovarsky		10	3
	(Chiari)	11	5	
	(Hedinger)		7	6(?)
1914.....	Wissmer-Kovarsky	29	10	4
1917.....	Crotti	?	?	?
1917.....	Vandenbergh		1	1
1917.....	Judd	105	6	?
1918.....	Binnie		1	1
1919.....	Kreglinger		1	1
1919.....	Simpson		?	?
1920.....	Von Rijssel		1	1
1920.....	Bouman	180	110	?
1921.....	Berry	12	2	?
1921.....	Wilson (U. S.)	98	19	
	(Mayo)	115	19	1 +
	(lit.)	524	39	
1921.....	Speese & Brown	25	3	

About January, 1919, the patient noticed an enlargement of the neck in the median anterior aspect. This increased rapidly in size, extending toward the right side. She was operated upon in June, 1920, about eighteen months after first noticing the tumor. The operation was not completed owing to the excessive hemorrhage. Only a small amount of tissue was removed which was not examined microscopically. At the time of admission to the Post-Graduate Hospital, February 25, 1921, the tumor was larger than before the attempted operation and more irregular in outline. There were no symptoms except those referable to the mechanical effect of the tumor.

TABLE 2

Spindle-cell Sarcomas Reported by Various Authors

Showing recognized presence of epithelial cells and inclusion of histological details in the reports. Where histological details are given this is indicated by + mark.

	Sarcoma	Epithelial Cells	Spindle Cells	Histological Details
Foerster...	1	+	+	+
Foerster...	1	+	+	
Foerster...	1	+	+	
Muller...	1	?	+	+
Doleris...	1	?	+	
Socin...	1	?	+	
Rose...	1	?	+	+ Eberth
Kautman...	1	+	+	+
Heath...	1	None	+	+
Maas...	1	?	+	Mixed cells
Tillaux...	1	None	+	+
Wollfer...	1	+	+	
Koch...	1	+	+	
Braun...	1		+	Mixed cells
Braun...	1		+	Mixed cells
Braun...	1		+	Mixed cells
Bowlby...	1	None	+	+
Moore...	1	None	+	+
Kobler...	1	+	+	
Shattuck...	1	?	+	
Plonnis...	1	?	+	
Jones & Battle...	1	?	+	
Orcel...	1	?	+	
Frerichs...	1	?	+	
Roux...	1	?	+	Niehus
Pick...	1		+	Secondary
Rabé...	1	?	+	Mixed cells
Reverdin & Buscarlet...	1	+	+	+
Tiffany & Lanier...	1	+	+	+
Kummer...	1	+	+	
Morf...	1	+	+	Mixed cells
Schiller...	1	?	+	
Schiller...	1	?	+	
Schiller...	1	?	+	
Firth...	1	+	+	Mixed cells
Cumston...	1	+	+	
Rotter...	1	+	+	
Lartigau...	1	+	+	
Papin & Saborianu...	1	+	+	
Saltykow...	1	+	+	
Ehrhardt...	1	+	+	
Muller & Speese...	1	+	+	
Kocher...	1	+	+	
Herrenschmidt...	1	+	+	
Michel...	1	+	+	
Porter...	1	None	+	+
Wissmer-Kovarsky...	1	?	+	+
Kovarsky...	1	+	+	
Kovarsky...	1	+	+	
Vandenberg...	1		+	+ Warthin
Binnie...	1		+	+ Welch
Kreglinger...	1	None	+	+
Von Rijssel...	1	?	+	Mixed cells
Berry...	1	?	+	
Mallory...	1	+	+	

Physical examination was negative except for the tumor of the neck. There was a tumor mass involving the entire right side of the neck extending from the angle of the jaw along the mandible two inches beyond the median line, overlapping the clavicle below and posterior to the anterior border of the trapezius muscle. The tumor was irregularly nodular and resilient. It was not attached to the skin. The skin over it was bluish in color with dilated veins. A pre-operative diagnosis of colloid goitre was made.

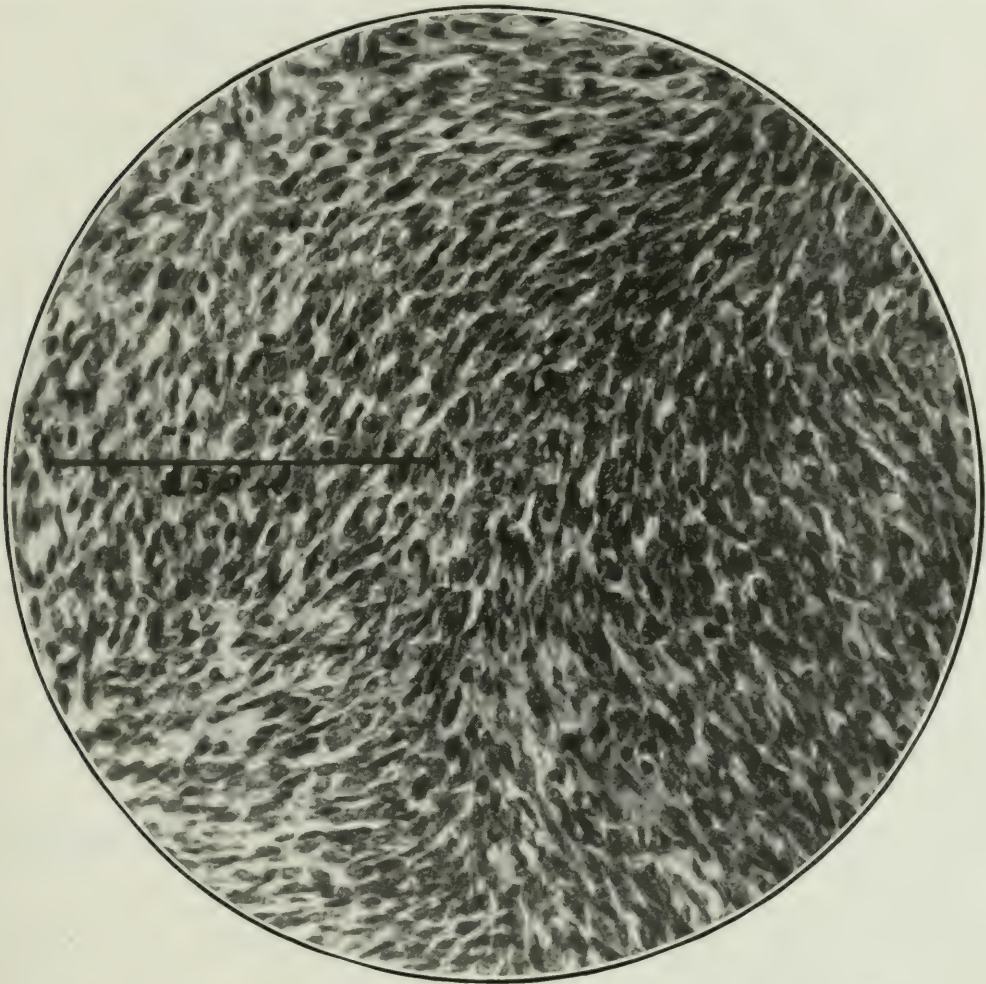


FIG. 1. Spindle-cell fibroblastic sarcoma of the thyroid gland. The structure of the tumor everywhere conforms to this type. Photograph of section stained with hematoxylin eosin.

Radiographic examination showed a large tumor in the soft structures in the right cervical region, of diffuse, even density without apparent bony attachment.

On March 3, the tumor was removed by Dr. Moorhead, the posterior capsule remaining. The operation lasted one hour and five minutes. The patient died ten hours later. Post-operative diagnosis was colloid goitre.

Tissue received at Laboratory was put in ten per cent. formalin solution. Later some of the pieces were transferred to Zenker's solution.

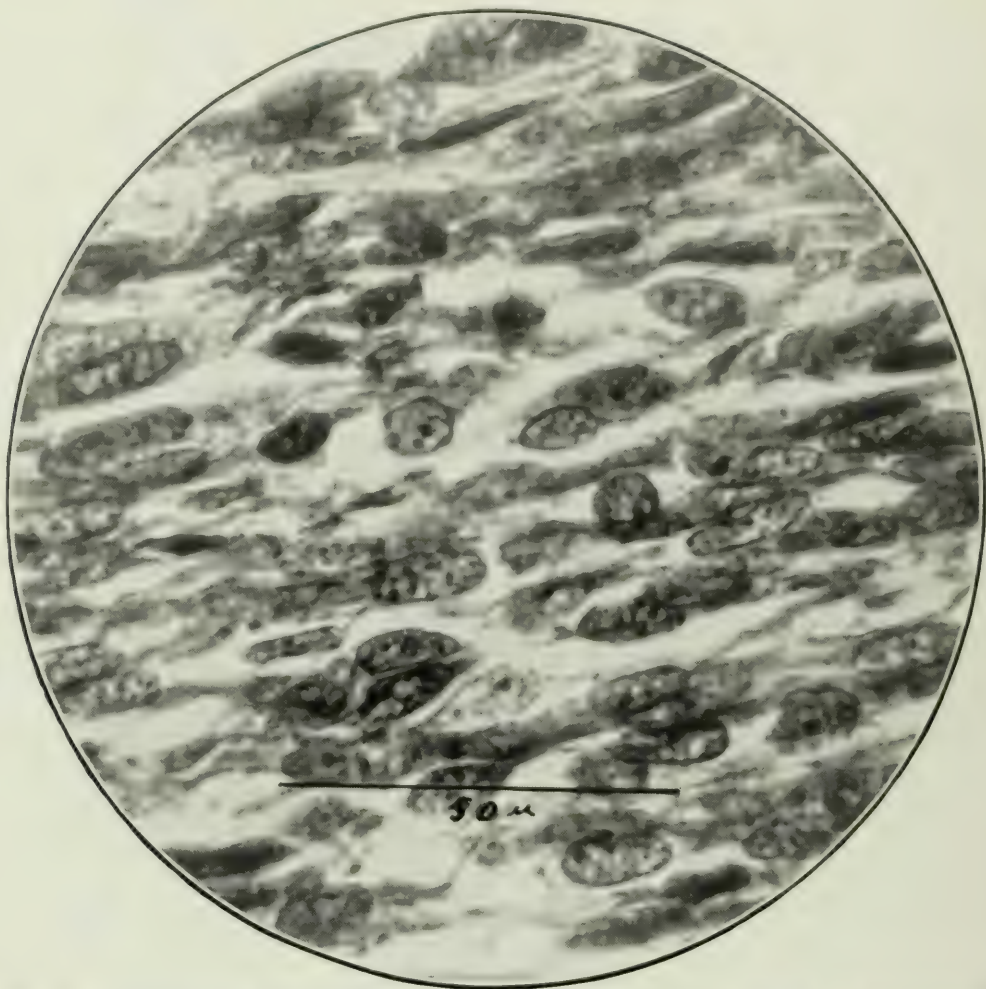


FIG. 2. Spindle-cell fibroblastic sarcoma of the thyroid gland. Photograph of a section stained with Mallory's connective-tissue stain.

Gross description: There are about twenty irregular fragments of fairly firm, pale grey tissue, total weight 255 grams. The largest pieces are 6 to 7 cm. in diameter. A few pieces are covered with a thin capsule, beneath which there are numerous irregular hemorrhagic areas. The tissue is somewhat brittle. The broken surfaces are coarsely serrated, the serrations suggesting coarse bundles of fibrous tissue. The cut surface is smooth and glistening, marked throughout by interlacing white fibre bundles separated by translucent streaks. There is nothing to suggest thyroid gland or colloid material.

Microscopic: Sections taken from many areas are identical in histological structure. They show sheets of fusiform cells closely packed. The cells are arranged in bundles several millimeters in diameter and appear in longitudinal, transverse and oblique sections. The bundles are separated by con-

nective tissue fibrils. The cell nuclei are generally fusiform in longitudinal and round in transverse section. The average diameter is about twice that of a red blood cell and the length two to five times the diameter. The cell body is relatively small and stains faintly. The nuclei vary in staining prop-

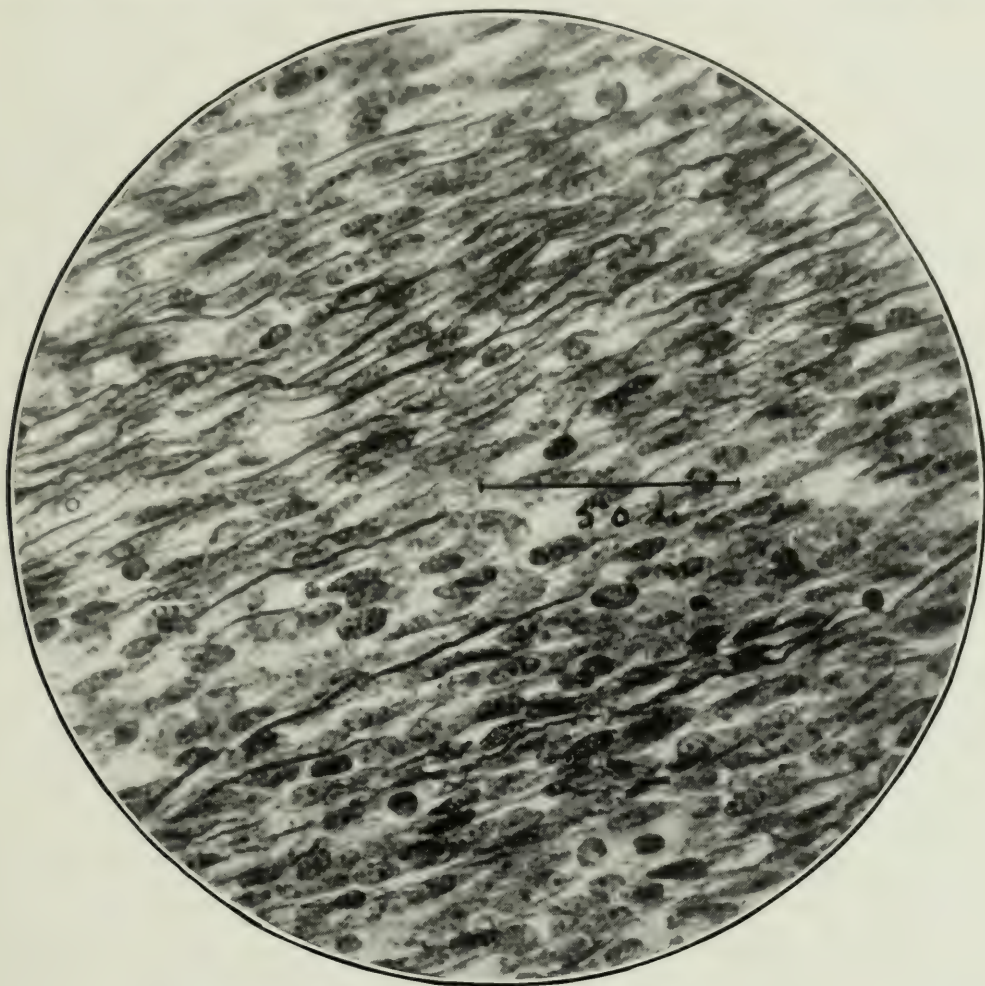


FIG. 3. Spindle-cell fibroblastic sarcoma of the thyroid gland. Intercellular fibrils are stained intensely black. Photograph of a section stained by the Maresch-Bielchowsky method.

erties; some are pale and vesicular and a few are pyknotic and compact. Occasionally mitotic figures are seen, but not in all oil-immersion fields. Usually one, but rarely four may be seen in a single field. The spaces between the cells are sometimes less and sometimes more than the cell diameters and are crossed by both coarse and fine fibrils. The blood supply is abundant in a few areas. The blood vessels appear for the most part as narrow branching channels between the cell bundles and as minute tubes between the cells. The channels are occasionally without definite walls and red blood cells are seen between the adjacent tumor cells. (See Fig. 5.)

The interest centers upon the fibrils between the tumor cells. With hematoxylin and eosin the fibrils are stained pink. With Van Gieson's stain they are pink and of the same nature as those forming the delicate walls of the blood channels, but areas having no blood channels show the fibrils between

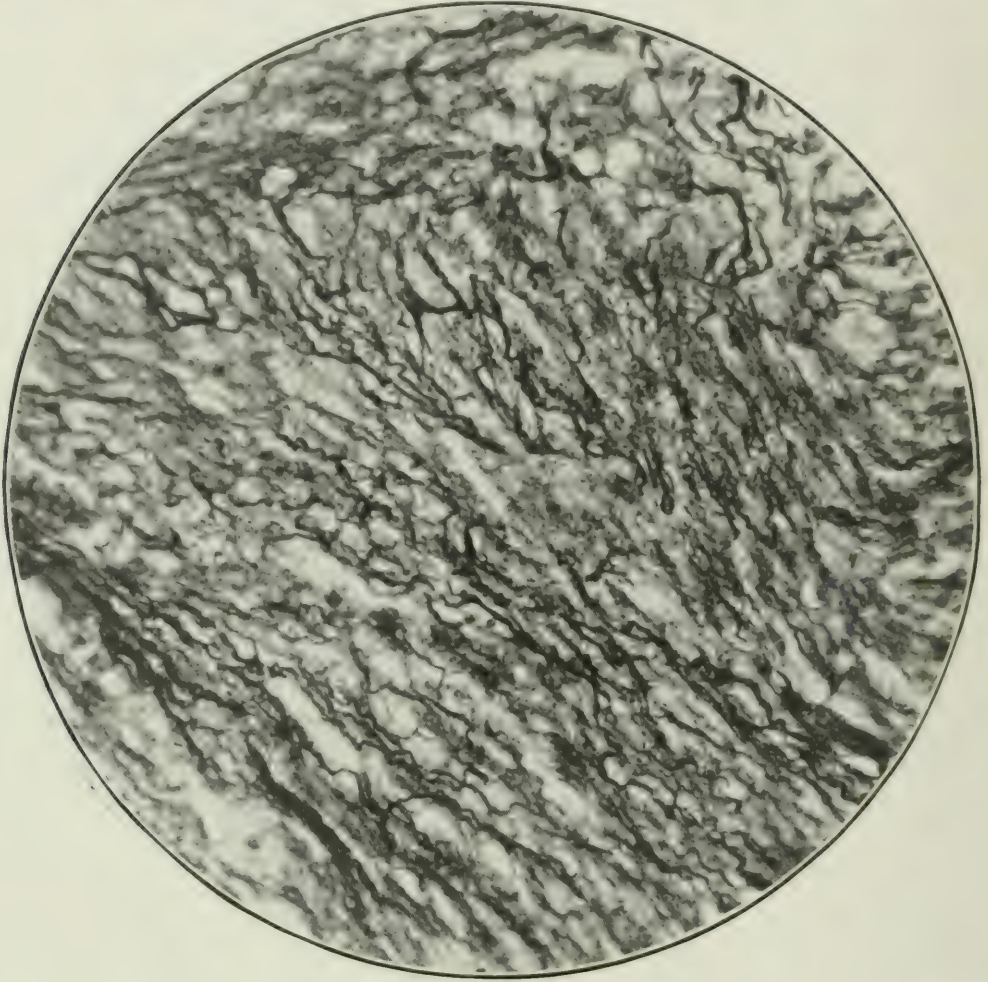


FIG. 4. Spindle-cell fibroblastic sarcoma of the thyroid gland. Intercellular fibrils are stained intensely black and nuclei are very indistinct. Photograph of a section stained by the Maresch-Bielchowsky method.

the cells. With Mallory's connective tissue stain the intercellular fibrils stain blue. In some areas they are numerous and between all the cells, but in other areas they are less plentiful, even scarce. There are also delicate red fibrils attached to the cells. Some cell bodies are opaque and stained diffusely bright blue, others are diffusely bright red. (See Figs. 2 and 5.)

With Maresch's modification of the Bielchowsky stain these fibrils stain intensely black and conform exactly to Kuro's description of connective tissue fibres as he demonstrated them for the identification of tumor cells. (See Figs. 3, 4 and 6.) With Weigert's resorcinofuchsin stain, elastic fibres are not found in the sections except in the walls of the largest blood channels.

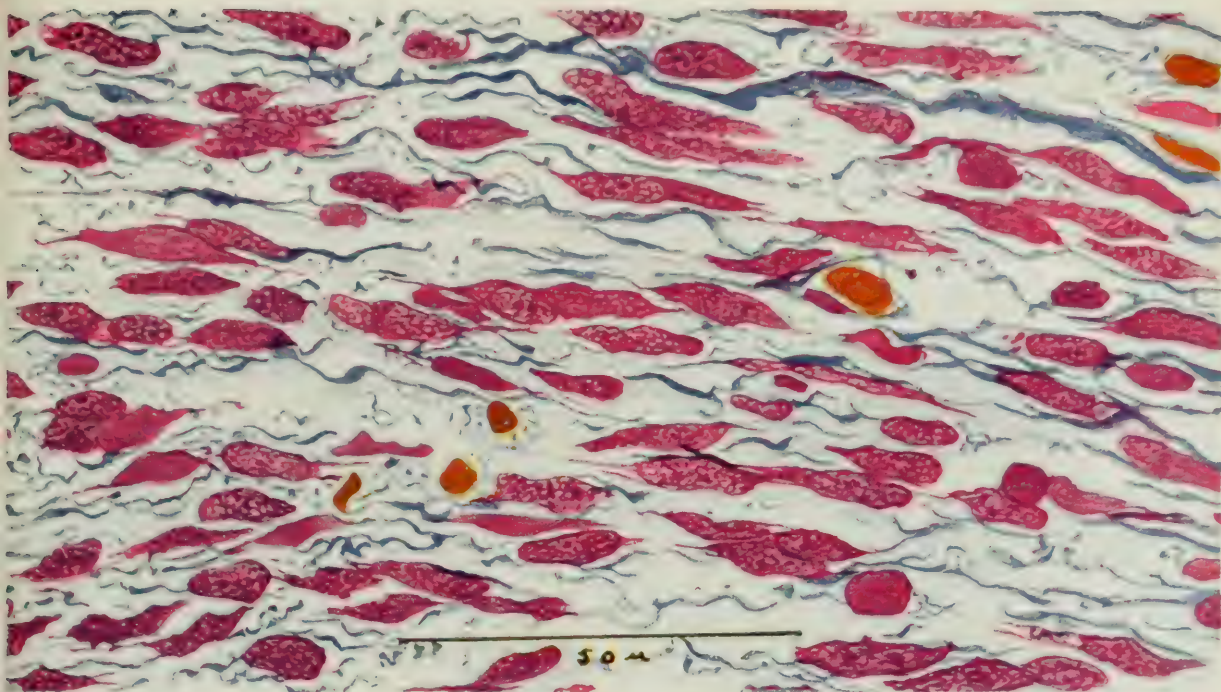


FIG. 5. Spindle-cell fibroblastic sarcoma of the thyroid gland. Intercellular fibrils are blue. Drawing with Zeiss objective 2 mm. Compensation-Ocular 6. Section stained with Mallory's connective-tissue stain.

In no section have we found epithelial cells and nothing to suggest alveolar arrangement. No colloid has been found.

We have attempted by the use of several staining methods, hematoxylin and eosin and Van Gieson, supplemented by those of Mallory and Bielchowsky, to demonstrate that the intercellular fibrils of this tumor are of connective tissue origin and that the spindle-cells of this tumor are of the same derivation. All stains of the tumor sections have been made with control sections of known tissue on the same slide and it seems reasonable to assume that the results may be depended upon as technically correct.

CONCLUSIONS

Most authors agree that the clinical aspect and gross appearance are not diagnostic of sarcoma of the thyroid gland and that the differentiation from carcinoma must be made by the microscope. Tumors without this examination cannot be accepted as sarcomas.

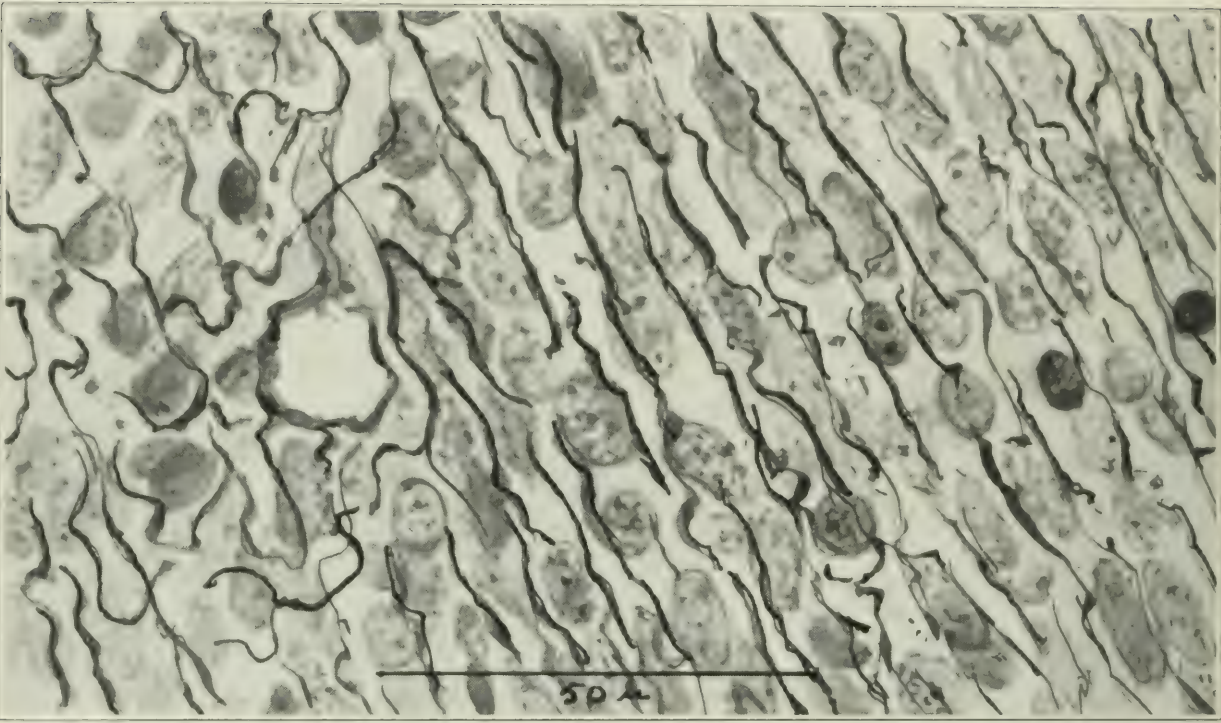


FIG. 6. Spindle-cell fibroblastic sarcoma of the thyroid gland. Intercellular fibrils are black. Drawing with Zeiss objective 2 mm. Compensation-Ocular 6. Section stained by Maresch-Bielchowsky method.

From the microscopic evidence there are possibly six reported cases of spindle-cell sarcoma of the thyroid gland of which two, namely, the tumor reported by Vandenberg and examined by Warthin and that reported by Binnie and examined by Welch, seem to be definitely established.

The necessary requirements for a positive diagnosis of spindle-cell sarcoma of the thyroid are the same as for diagnosis of sarcoma in any other locality. All sarcomas should show intercellular connective tissue fibrils, and tumors not conforming exactly to these requirements are not true sarcomas and should not be so designated.

The tumor reported here conforms to these requirements and is, therefore, a true spindle-cell fibroblastic sarcoma of the thyroid gland.

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Discussion:

DR. LARKIN: I was very much interested in the presentation of primary tumors of the thyroid. The completeness of the report is only to be appreciated by those who have had ample opportunity to look over tumors of this particular type. The very exhaustive manner in which Dr. Meeker has presented this subject is amazing, and leads us to the conclusion that the final

diagnosis and differentiation of tumors of the thyroid is only to be made by the microscope. One of the slides looked like the tumor which was reported by Lartigau several years ago, and at that time the observation was made that they were of a definite type and belonged to the spindle-celled variety. We are wont to look at tumors of the thyroid, and dismiss them as colloid goiters, and I think a more extensive study should be made of these tumors which are dismissed by pathologists as belonging to the ordinary type of adenocarcinoma. The presentation is certainly a very excellent one from the standpoint of the differentiation of tumors of the spindle-cell variety in the thyroid gland.

DR. EWING: Confronted by this formidable list of authorities cited, and especially by the very thorough and convincing study of Dr. Meeker's case, there would seem to be little ground remaining for the statement that the existence of primary sarcoma of the thyroid remains to be demonstrated. Certainly one must admit that if there is a primary sarcoma of the thyroid, her case is one, if not the first one, fully proven.

However, there is always a defensive argument even in the most hopeless situations. It may be pointed out that the earlier authors cited were all positive about their diagnoses of sarcoma; later ones were not quite so sure, one critical observer concluding merely that there are sarcomas of the thyroid. Recently one finds more frequent admissions that the differential diagnosis between sarcoma and carcinoma is very difficult in the thyroid, and an increasing number of mixed sarcomas and carcinomas is mentioned, which shows that the study of tumors of the thyroid has become more critical. Now this story reflects my own experience with sarcoma of the thyroid. Some years ago I saw Lartigau's case, and was not satisfied that it was true sarcoma on account of the presence of certain cells which seemed to be epithelial. It was at least a carcino-sarcoma. In so many cases of apparent sarcoma of the thyroid I have found areas of polyhedral cells and transitions of polyhedral epithelial cells into spindle-cells, that I have become quite skeptical regarding the usual diagnosis of sarcoma in this organ. It seems quite certain that no one should venture the diagnosis of sarcoma of the thyroid without considerable search for areas of epithelial cells, since in tumors of this gland epithelial tumor cells are particularly prone to assume a spindle form.

Moreover, I think the time is passed when one can assert that a tumor is a mesoblastic sarcoma simply because it presents spindle cells. Not even the demonstration of various intercellular fibrils will suffice for this purpose. One must offer in addition some evidence regarding the histogenesis of the tumor, such as we have for periosteal and neurogenic sarcoma. Such evidence is not available for sarcoma of the thyroid. Yet one cannot presume that the connective tissue of the thyroid gland is immune to malignant tumor growth. Sarcomas probably arise in this gland as in others, but the general pathology of the thyroid does not reveal the same satisfactory basis for recognition of sarcoma as in many other situations. Until some one in a series of cases can trace the histogenesis of sarcoma of the thyroid I think the final proof of the existence of such a tumor is wanting. This proof has been fur-

nished for many other sarcomas, and the thyroid need be no exception.

In the case of Dr. Meeker's tumor I had the opportunity to study the sections. We could find no trace of epithelial cells in many sections, but I was struck with the resemblance of the histological picture to that of neurogenic sarcoma, with intertwining fibrils, and having no better resort in an embarrassing situation, I ventured to suggest that it was a neurogenic sarcoma arising from the nerve structures of the gland.

There is one particular group of so-called sarcomas of the thyroid, probably figuring in the literature, which seem to have no relation to true mesoblastic sarcomas. These are the various stages of sclerosis exhibited by Riedel's "iron-hard struma," cellular stages of which I believe are described by Hashimoto (Langenbeck's *Archiv*, xcvi, 219). These cases seem to represent cellular and sclerosing stages of a benign lympho-granuloma of the thyroid. I have seen both phases in the same tumor. They may greatly resemble a sarcoma but have nothing to do with true mesoblastic sarcoma.

Therefore, while Dr. Meeker has succeeded admirably in demonstrating a sarcoma in the thyroid gland, I must continue to feel that until the matter of histogenesis has been cleared up, the existence of a true mesoblastic sarcoma arising from the connective tissue of the thyroid gland remains uncertain.

DR. MEEKER: I wish to emphasize that many sections were taken; more than a hundred sections were stained, and we have found no evidence of epithelial cells. I would like to ask Dr. Ewing what further steps are necessary in this demonstration, and ask him to suggest what I should do next.

DR. EWING: I do not think one can do anything more with this case. This is the best observation recorded which deserves consideration as a primary sarcoma of the thyroid. It may however be a neurogenic sarcoma. The histogenesis of a tumor cannot be demonstrated on a single case. One has to lay a foundation for sarcomatous processes in the thyroid from the general pathology of the gland, and then one has to collect a series of tumors from which one can demonstrate the beginnings of the tumor in one structure. That is the nature of much of the study of tumors that is going on today.

The importance of such studies is revealed in the fact that where the histogenesis of a group of tumors has been determined, as of neurogenic or osteogenic sarcoma, it usually transpires that the tumors thus identified show specific etiological, histological, and clinical features, which render them specific neoplastic diseases.

DR. MEEKER: I want to make it clear that I did not intend in any way to oppose Dr. Warthin and Dr. Welch to Dr. Ewing.

THE COLORIMETRIC DETERMINATION OF THE
HYDROGEN ION CONCENTRATION

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The importance of a knowledge of the hydrogen ion concentration of various biological fluids such as urine, blood, bacteriological culture media, etc., has come to be quite generally appreciated. The difficulties encountered in making the determination, however, have restricted its use to specially equipped laboratories. The electrometric methods still require expensive apparatus and special training, but the colorimetric method has been greatly improved and simplified, especially at the hands of Sørensen and Clark. With this method, as generally employed, a series of tubes are made up containing buffer solutions with pH differences of 0.2 for the range of the indicator. These are employed for comparison with the unknown. Obviously the preparation of such a series of standards is time-consuming and their use rather cumbersome.

It has previously been pointed out¹ that with the use of two wedges in a modified Hellige colorimeter, it is possible to obtain all the shades of color in a given indicator from the acid to the alkaline side, when one wedge is filled with an acid solution of the dye and the other with an alkaline solution. These may be made with buffer solutions of a definite pH, or as we have recently observed, of solutions of the indicator made sufficiently acid or alkaline to produce a complete change in the color of the indicator. Obviously it is essential that the concentration of indicator should be the same in both standard and unknown. Where it is desired to read very small differences in pH over only a limited range it is best to make the standards of a definite pH just outside of the range to be covered. With this technic it is possible to make readings which are accurate to a difference of roughly \pm pH 0.02.

Barnett and Barnett² and Gillespie³ have employed similar

principles in the colorimetric measurement of the hydrogen ion concentration. The former authors employ a low, narrow, rectangular glass box having a diagonal glass partition, one being used for the acid and the other for the alkaline solution of the indicator, while the latter achieves the same result by having a small movable cup fitted over the plunger but inside the cup of a Duboscq type colorimeter.

The use of wedges which are individually movable provides a much more flexible system.⁴ The reading of the wedge containing the dominant color of the dye, *e.g.*, the red in phenol red, characterizes the hydrogen ion concentration, the yellow wedge being employed simply to obtain a correct color match. This being the case it may also be employed to correct for any slight error due to extraneous yellow pigment in the unknown.

At the author's suggestion E. Leitz, New York, has constructed a new wedge colorimeter for these determinations. Briefly the instrument comprises a brass box 30 cm. in height, containing a rack and pinion arrangement for three wedges, the movement of the wedges being entirely within the closed box. Readings are taken from 100 mm. scales which emerge from the top of the instrument as the wedges are raised. The instrument is provided with prisms and an eyepiece in front and a milk-glass plate in back for the entrance of light. For the latter a small lamp box may be substituted. A door at the side gives access to the wedges and to the cup for the unknown which is mounted on it. Two wedges provide for biocolorimetric work as in the pH determination. However, to obtain a perfect match with unknown solutions which are slightly turbid or colored a third wedge may be used.

Since giving a preliminary description of this instrument,⁴ it has been improved by the replacement of the Helmholtz prisms with the type of prisms employed in instruments made on the Duboscq pattern. Thus modified the light passes more nearly through the center of the wedges and cup, furnishing a better field for comparison. The lamp box as now constructed uses only reflected light, which passes through a very thick daylight glass. The small nitrogen bulb is set below the field of vision,

the reflecting surface being covered with aluminum paint. The light obtained from the present lamp is quite equal to daylight in quality, and superior to it in intensity.

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CHEMICAL CHANGES IN THE BLOOD IN PNEUMONIA

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It is a fact of common knowledge that the development of pneumonia in human subjects entails a more or less severe impairment of renal function. That this disturbance of kidney efficiency cannot be attributed to a direct transfer of the infection to the kidneys is evident from studies upon the urine. With the object of determining the mode of production of this renal impairment and its prognostic significance, the study of the chemical changes in the blood was made in a series of fifty cases of pneumonia of various types. An attempt was made to obtain the blood specimens at frequent intervals throughout the course of the disease, but in the majority of cases this proved impossible, since the patients did not enter the hospital until the pneumonia was well advanced. The observations made include determinations of the nonprotein and urea nitrogen, uric acid, creatinine, sugar and chlorides of the whole blood, and the carbon dioxide combining power of the blood plasma.

It was noted that about the time of the crisis the nonprotein nitrogen was definitely increased from 34 to 156 mg. per 100 c.c. This increased nonprotein nitrogen was found to be due to a rise in the undetermined fraction, and apparently was caused by an accumulation of complex protein catabolites producing

a toxemia. This toxemia resulted in a damage to kidney function. Following the increase in the nonprotein nitrogen the uric acid concentration of the blood rose from 3.8 to 11 mg., and subsequently there was a rise in the urea nitrogen to 20 mg. or more. When the urea nitrogen had reached this level a definite accumulation of creatinine was noted. In a few instances the creatinine exceeded 5 mg. per 100 c.c., and death in these cases could undoubtedly be attributed to the severe impairment of renal function. The order of retention in the blood of the nitrogenous waste products was analogous to that observed in nephritis of the interstitial type, first, the uric acid, secondly, the urea, and finally, the creatinine. Although the secondary kidney damage may not be the only cause of death in pneumonia, it may be said that the prognosis from the standpoint of renal function becomes grave when the urea nitrogen of the blood exceeds 25 mg. per 100 c.c.

The normal concentration of the chlorides of the whole blood varies from 0.45 to 0.50 per cent. (as NaCl). A significant decrease in the blood chlorides from 0.288 to 0.425 per cent. was found in the majority of the patients before the crisis. It was not possible to establish any definite relation between the decrease in the blood chlorides and any of the clinical manifestations of the disease. At the time of the crisis, the chlorides quickly rose to a level exceeding 0.50 per cent., and gradually dropped back to within normal limits. In a few cases subnormal blood chlorides were found with a retention of the nitrogenous waste products.

Pneumonia was found to produce a slight decrease in the carbon dioxide combining power, 45 to 50 volumes per cent. This apparent mild acidosis is no doubt due to a deficient elimination of carbon dioxide by the lungs. However, when the blood showed a marked accumulation of the nitrogenous waste products, the carbon dioxide combining power was found to be diminished to 20 to 30 volumes per cent.

COMPATIBILITY OF BLOOD FOR TRANSFUSION

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The knowledge of isohemagglutinins and isohemolysins is not of recent date. In 1901 Landsteiner¹ divided the human race into three groups according to the action of their serums and cells when brought into contact. Group I comprised all individuals whose cells were agglutinated by no serums and whose serums agglutinated all other cells. Group II was made up of those whose cells were agglutinated by serums of Groups I and III, and whose serums agglutinated cells of Group III. In Group III were placed those whose cells were agglutinated by serums of Group I and II and whose serums agglutinated cells of Group II. It was not until 1907 that Jansky² announced the recognition of still one more group, which he called Group IV, composed of a very limited number of people, whose cells were agglutinated by all other serums and whose serums agglutinated no cells. The designation of human blood groups as above defined is now known as the Jansky classification.

Moss in 1910 and 1911 confirmed these findings and reported that pathologic as well as normal blood could be classified into four groups. Unfortunately Moss interchanged Groups I and IV of Jansky's classification so that the Jansky Group IV is the Moss Group I and Jansky Group I is Moss Group IV. Thus there are two classifications in use at this time, though the Jansky classification has been adopted by the American Association of Immunologists and the American Association of Pathologists and Bacteriologists and would appear to be the logical choice.

With known serums of Group II and Group III it is a very simple matter to group all individuals. A drop of serum II is put on one end of a glass slide and a drop of serum III on the other end. A drop of blood of the person to be tested is mixed with the different serums. Usually any agglutination is visible

to the naked eye, but the preparation should always be examined with the low power of the microscope.

Cells of different individuals differ markedly in the amount of agglutinin they contain. Likewise serums also vary in agglutinating power, some being quite low in their agglutinin content. It can thus be seen that for correct grouping, it is essential to select for standard test serums, those with strong agglutinating power. To ten parts of serum is added one part of 10 per cent. sodium citrate in 0.9 per cent. salt solution and one part of 5 per cent. carbolic acid and the final product put up in sealed ampoules. It keeps its agglutinating properties for many months.

In those cases that come up for transfusion, if time permits, a mutual compatibility test should be done. This is done by obtaining 4 or 5 cubic centimeters of defibrinated blood from both patient and selected donor. The cells and serum are separated, the cells washed and a 1:20 suspension in salt solution made of each. Six small tubes are set up. Into each of the first three is placed 0.1 c.c. of the donor's red blood cell suspension; into the next three a similar amount of patient's red blood cell suspension; into the first and fifth tubes 0.4 c.c. of the patient's serum, and to the second and fourth 0.4 c.c. of the donor's serum. All the tubes are made up to the volume of 1 c.c. with 0.9 per cent. salt solution. These tubes are shaken and incubated for two hours at 37° C. and let stand at room temperature over night, which insures a more even setting of the cells than in the ice box. The readings taken on the tubes are for agglutination and hemolysis. Usually within one half to one hour after incubation the test can be read for agglutination. This test serves as a check upon the grouping and assures the patient of a compatible donor, as incompatibilities within the group, although infrequent, do nevertheless occur.

Only two such incompatibilities within the group have been met with in our mutual compatibility tests, both in Group IV Jansky, one a young woman of twenty-one, and the other a child of four years. The young woman had pernicious anemia and at the time there was available only one donor of her group.

The donor's serum slightly hemolyzed the patient's cells. There was no apparent agglutination present in the tube. As this donor of her own group injured her cells less than donors of other groups and it seemed imperative that she be transfused, she was given 150 c.c. of blood. The subsequent reaction was very severe but not lethal and was followed by improvement.

In the case of the child only a grouping had been done and a professional donor called in. After 40 c.c. of blood had been given the transfusion was stopped on account of the condition of the patient. A request was then made for the mutual compatibility test with the donor used and in this test the patient's serum agglutinated and hemolyzed the donor's cells markedly. Another Group IV (Jansky) donor was found to be perfectly compatible.

One other case of interest has been met with, a pregnant woman who came into the hospital to be transfused on account of a pronounced anemia. This was her second pregnancy. During the first she was also very anemic and aborted about the fourth month, after which the anemia disappeared only to reappear during her second pregnancy. In this case grouping was not done, but mutual compatibility tests were done, trying out three brothers. All proved to be incompatible and furthermore the patient's serum was found to agglutinate her own cells. Her blood was then tested against bloods from donors of each group and found to be incompatible. No transfusion was done. At the end of the seventh month her red corpuscles had decreased to 800,000 per cu. mm. and miscarriage took place. Some months later she returned, apparently in good health. She had 3,500,000 red blood cells per cu. mm. and was found to belong in blood Group II.

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FATTY DEGENERATION OF THE HEART

A. M. MASTER, M.D.

The clinical and pathological diagnosis of "fatty heart" or of the heart the seat of "fatty degeneration"* is still too commonly made. A decade ago it was even more frequently diagnosed than it is now. Broadbent¹ described the etiology, symptoms, physical signs, prognosis and treatment of fatty degeneration of the heart. He says, "No form of heart disease is regarded with so much apprehension as fatty degeneration. More than any other, it causes with it the dangers of sudden death and the liability to angina pectoris."

Hirschfelder² also described the symptoms and signs of the heart of fatty degeneration. He says, "The most characteristic symptoms associated with the condition are those of general debility and feebleness, more or less languor and somnolence as a rule without marked cardio-respiratory symptoms except shortness of breath on exertion. The pulse is usually small, rather collapsing and feeble, the blood pressure is below normal . . . the pulse rate is increased. On physical examination the heart may be either normal or dilated, the sounds either feeble and distant or short and sharp, the apex impulse may or may not be well marked. The liver and spleen are often enlarged. There is sometimes edema of feet and ankles."

We are told that the tone of the cardiac muscle is diminished, that patients with fatty degeneration of the heart are very sensitive to digitalis and are frequently injured by it. Sudden death from overdose of this drug or from acute cardiac overstrain is more common in patients with fatty degeneration of the heart than in almost any other condition and finally spontaneous rupture of the heart is relatively frequent in this condition. And so pages have been written.

In summary, however, Hirschfelder frankly states that none

* We distinguish here between fatty degeneration of the heart with which this paper deals solely and fatty infiltration in which fat is present beneath the epicardium, or penetrates between muscle bundles even as far as the endocardium.

of the symptoms is "either constant or characteristic" and the diagnosis may have to be made by inference only. As Krehl³ says, there is no clinical sign for the diagnosis of fatty degeneration of the heart.

We believe that the clinical diagnosis of fatty degeneration should only be made on etiological grounds, *e.g.*, in phosphorus poisoning, pernicious anemia, etc., where we expect this finding. Otherwise to make this diagnosis during life is a very uncertain proceeding.

Having discussed fatty degeneration from the clinical aspect let us now look at the question from a pathological point of view. It is trite to state that necropsy findings must be in great part the criteria upon which diagnoses rest. Undoubtedly then, the frequency of the diagnosis of "fatty heart" is based upon the same frequency with which this type of heart is found on the post-mortem table. We are told by the highest authorities that fatty degeneration of the heart is a common pathological condition.

The etiology² is given as alcoholism, primary and secondary anemia, after hemorrhage, in association with myocarditis, valvular and other cardiac lesions, in most infectious diseases, in miners, smelters, and in many metal workers, etc.

Sir William Osler⁴ in discussing the anatomical basis of cardiac insufficiency says, "Fatty degeneration is a very common condition. It is found in the failing nutrition of old age, of wasting diseases and of cachectic states; in prolonged infectious fevers in which it may follow or accompany the parenchymatous changes. In pernicious anemia and in phosphorous poisoning the most extreme degrees are seen. . . . Lastly, in the hypertrophied ventricular wall in chronic heart disease fatty change is by no means infrequent. . . ."

"There appears to be a special proneness to fatty degeneration in the heart muscle which may perhaps be connected with its incessant activity."

It is our contention that the diagnosis of fatty degeneration of the heart is made too frequently in the pathological laboratory. Here the criterion of this condition is the presence of fat

within the muscle-cell. Adami says, "Fatty degeneration of the heart is a common condition characterized by the presence of minute globules of fat in the muscle fibers which are deposited in small droplets generally in line of the longitudinal fibrillæ of the cell." Years ago, then, from the work of Virchow,⁶ Adami⁵ and others we have all been taught that visible fat in the cardiac muscle cell was pathological, *i.e.*, fatty degeneration was present.

To prove our stand that fatty degeneration of the heart is diagnosed too often we decided to examine a series of pathological hearts and to utilize normal human hearts as controls.

For our pathological hearts we examined post-mortem the hearts of twelve patients from the medical services of Dr. L. A. Conner and Dr. W. L. Williams at the New York Hospital. These patients had been in the hospital as "cardiacs," *i.e.*, they were cases of myocardial or valvular disease or both, and the symptoms from which they suffered were primarily ascribed to their hearts. They all died with the classical symptoms of myocardial failure. The following is the clinical history typical of any one of these cases. The pathological findings in regard to presence or absence of fatty degeneration is also typical of all the hearts.

CASE 1. Chronic myocarditis. The patient, 57 years old, was admitted to the Hospital on March 3, 1921, and discharged on April 25, 1921. He entered the hospital complaining of dizziness, pain in abdomen and swelling of the legs. He gave a long history of alcoholism and for the past five years had dyspnea on exertion and precordial pain, rarely with fainting attacks.

His heart was enlarged, 13 cm. to the left in the sixth space and 2 cm. to the right in the fourth space. The heart sounds were very poor in quality and distant, with extrasystoles. The rate was slow, 50 to 60.

The blood pressure was systolic 140, diastolic 90.

The urine showed a heavy trace of albumin, hyaline and granular casts, and specific gravity of 1.020.

The blood urea was 40 mg. per 100 c.c. of blood.

The autopsy findings were chronic parenchymatous nephritis, kidney infarcts, general atherosclerosis, chronic myocarditis (replacement fibrosis), hypertrophy of heart, congestion of liver, and chronic perisplenitis.

Gross examination of the heart showed on the surface of the organ a considerable increase of the fatty tissue. The heart was much enlarged. No areas of fibrosis were observed. The valves were negative, except for very slight thickening of the edge of the mitral valve. The coronaries were markedly thickened and calcified and narrowed throughout.

Microscopical examination of the heart revealed connective tissue replace-

ment in the region of the left apex and also in the right ventricle. The septum showed a moderate degree of fibrous replacement. There were a few small round cell foci at the pericardial surface of the left ventricle, and rarely in the muscle itself.

Innumerable fat droplets were found in large quantities in the muscle cells proper (see figure). These were arranged in the classically described positions for fatty degeneration, *i.e.*, in longitudinal and transverse rows between the muscle fibrillæ and also areas of muscle cells filled with fat alternated with those practically free from this tissue.

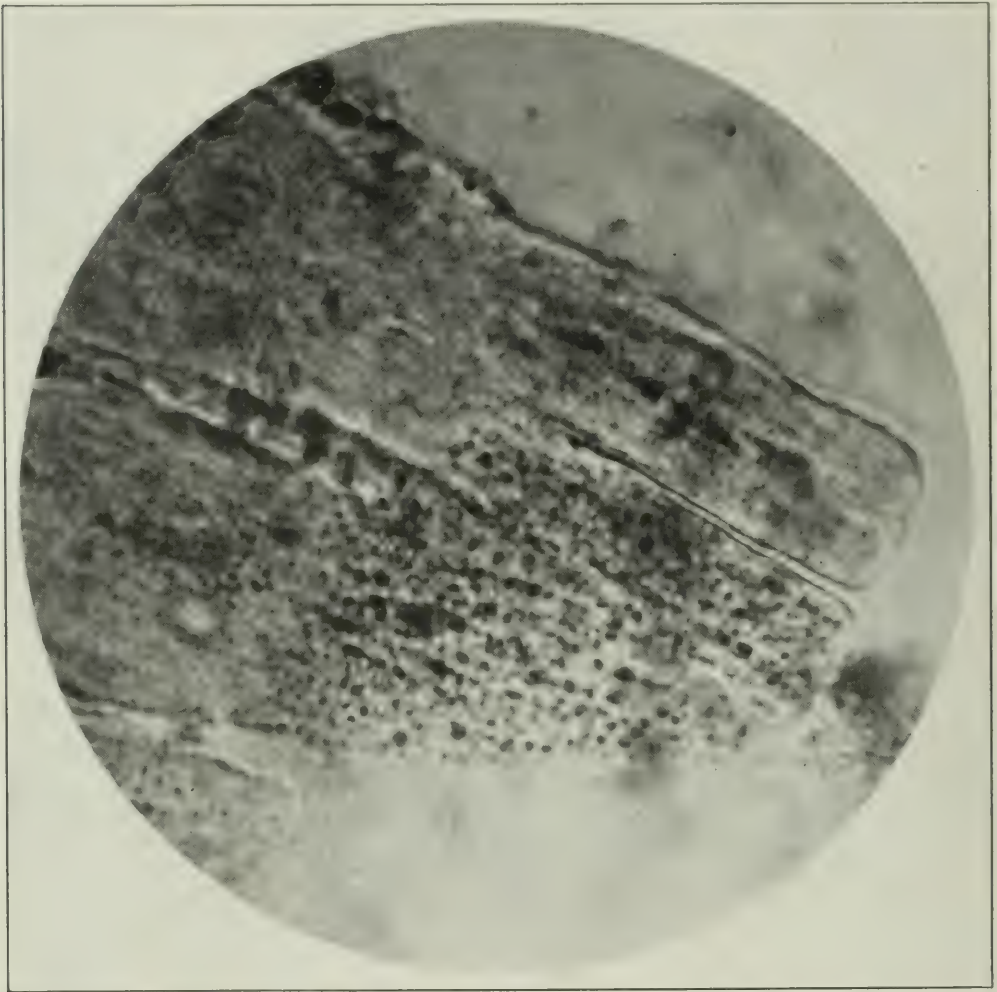


FIG. 1. Case A. Ventricular septum. Scharlach R stain. Carmine Red fat droplets (black in microphotograph) in longitudinal rows between the fibrillæ of the muscle cell and arranged transversely (on either side of Krause's membrane).

Another modern writer⁷ who correlated the electrocardiographic findings during life with the pathological condition of

the cardiac muscle at death in describing five cases of heart failure reported, "Marked fatty degeneration" in each case! If one opens to any one of the well-known text-books^{8,9} in pathology he will find drawings and photographs illustrating fatty degeneration of the heart muscle which exactly duplicate the pictures we obtained in the hearts of every one of our series. Our Scharlach R



FIG. 2. Text-book illustration of fatty degeneration of the heart. (From Stengel and Fox: Text Book of Pathology, 1921, Ed. 7, p. 503.)

stain demonstrated the minute red droplets in every heart we examined. Previously we may have believed as other writers did that visible fat is pathological but when every heart depicted this finding our opinion was strengthened that this view was incorrect. Hence we had recourse to our series of controls. This is the crux of the matter. If the normal hearts evidenced no fat droplets in the muscle cell we could say that this finding

was pathological. However, if the controls showed fat granules in human cardiac muscle to be a normal finding then our entire conception of fatty degeneration of the heart would have to be revised, pathologically and clinically, because the latter depended for proof on the necropsy states.

Hence we obtained thirteen hearts at the Bellevue Morgue from individuals who had met sudden, violent death by bullet or stab wounds, etc., and who at autopsy showed no abnormality that was apparent to the unaided eye. These people ranged from eight to fifty-six years, the average age being thirty-two years. Sections were taken from each ventricle, septum and auricle. The tissue was fixed in formalin and within twenty-four hours

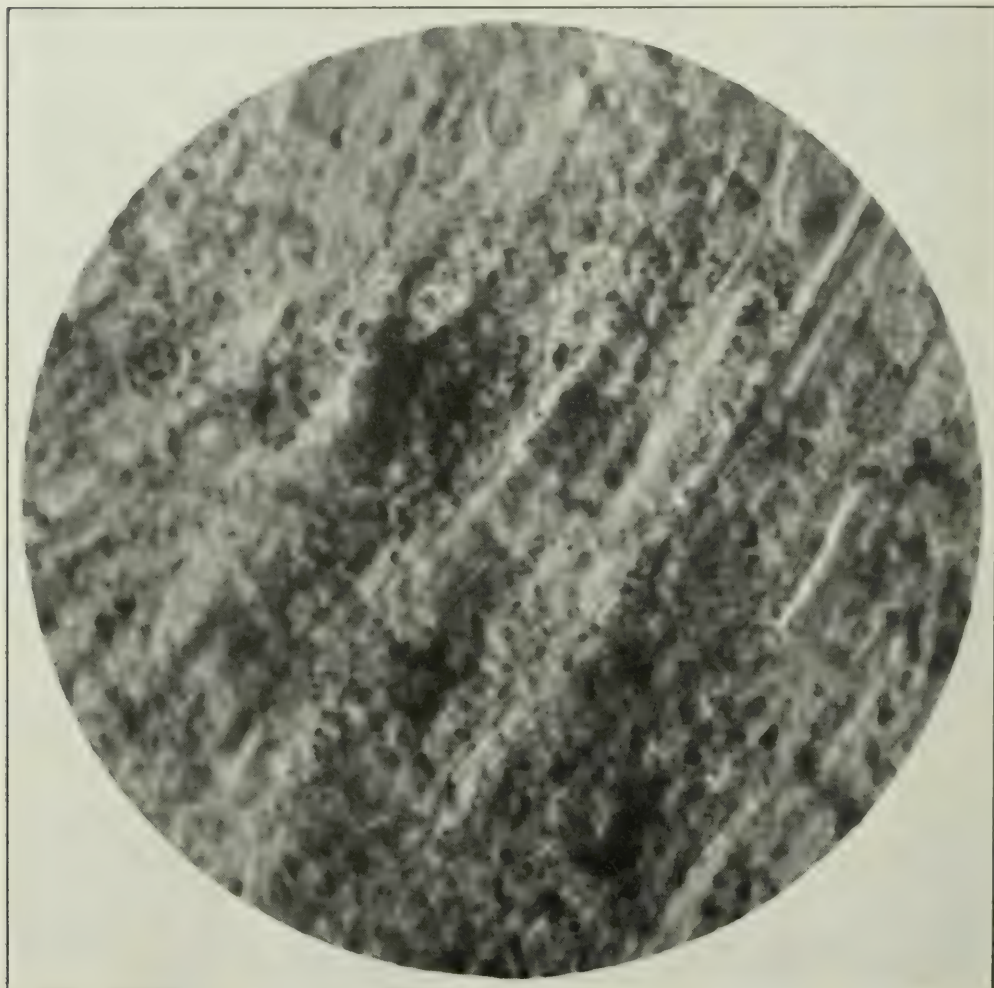


FIG. 3. Case D. Osmic acid stain. Results similar to Scharlach R (see Case A).

Case No.	Age	Sex	Color	Cause of Death	State of Nutrition at Autopsy	Presence of Diffuse Red Fat Droplets in the Muscle Cell between the Fibrille arranged in Longitudinal and Transverse Rows	Presence of Golden Brown Pigment at the Poles of the Nuclei, i.e., Pigment of Brown Atrophy
A	33	Male	White	Blackjacked, i.e., skull fracture, died within few hours	Good	Large quantity	Large quantity
B	45	Male	White	Stab wound of heart. Died immediately	Good	Slight or moderate amount	Large quantity
C	45	Male	White	Fracture cervical vertebræ. Died in few hours	Good	Present in some areas	Large, coarse, brown, bipolar pigment
D	23	Female	White	Cerebral hemorrhage died either immediately or within few hours	Very good	Abundance of granules	Good many granules
E	40	Male	White	Fracture of skull. Died in 3½ hours	Good	Abundance of granules	Good many granules
F	31	Female	White	Clinical diagnosis not made	Somewhat emaciated	Abundance of granules	Good many granules
G	20	Male	White	Shot to death. Died within 1 hour	Good	Very few granules	Good many granules
H	42	Male	White	Acute alcoholism	Good	Moderate amount	Very many granules
I	32	Female	Black	Died in few hours from hemorrhage after attempted criminal abortion	Good	Moderate amount	Very many granules
J	34	Female	Black	Acute alcoholism	Good	Great many granules	Very many granules
K	56	Male	White	Cerebral hemorrhage from blow	Good	Great many granules	Very many granules
L	15	Male	White	Shot to death. Died instantly	Good	Many granules	Moderate amount
M	8	Male	White	Run over by truck. Died in few hours	Good	Many granules	Moderate amount

frozen sections were stained with a saturated solution of Scharlach R dye in equal parts of 70 per cent. alcohol and pure acetone. The technique followed was that given by Mallory and Wright.¹⁰ At the conclusion of the experiments we stained one of the hearts with osmic acid (formalinized material placed in Marchi's fluid and cut by the freezing microtome). The results obtained were similar to those with Scharlach R. In regard to the Scharlach R we found small red droplets of varying sizes in the sarcoplasm of the cardiac muscle cells. These were arranged in longitudinal and transverse rows, the longitudinal droplets appearing between myofibrillæ. The number of granules varied. Some hearts were stained diffusely and uniformly, some scarcely at all and commonly there were groups of cells which took the stain well while in the immediate vicinity were cells which contained little, if any, fat.

The so-called pigment of brown atrophy, which is located at the poles of the nucleus and is supposed to be an indication of senility of the muscle, was stained yellow, yellow-brown, or golden-brown with Scharlach R. At first we found it difficult to distinguish between it and the diffuse fat droplets but after some experience we were able, in practically every case, to differentiate between the coarser brownish bipolar granules and the smaller red fat droplets distributed diffusely throughout the cell and arranged in longitudinal and transverse rows. With osmic acid the bipolar pigment was stained light brown whereas the fat granules were intensely black.

Hofbauer¹¹ in 1905 described visible fat in normal human fetal muscle. Bell¹² in 1912 first showed that visible fat is normally present in the cardiac muscle of the common laboratory mammals.

He also demonstrated that the quantity of visible fat is increased when fatty foods are given and diminished when the animals are starved. Wegelin¹³ found fat in the cardiac tissue of rats. He also examined the heart of an insane man who had jumped out of the window and found fat in quantities, although the organs appeared to be normal at autopsy. He expressed the belief that fat could be demonstrated microscopically in normal human heart muscle. Eyselin¹⁴ of Berlin did not agree with this.

H. Hays Bullard¹⁵ in 1912 stated that although Scharlach R was not specific for neutral fat (Scharlach R and Sudan III stain neutral fats, fatty acids,

soaps and lipoids with varying degrees of intensity) and although he did not believe that all the colored droplets in mammalian cardiac muscle were neutral fat, yet he thought that most of them undoubtedly were.

In a subsequent communication Bullard¹⁶ showed that there is microscopically demonstrable fat in the normal cardiac tissue of rats, cats, dogs, hogs, oxen and sheep. More than two hundred animals were investigated. The fat droplets in the sarcoplasm were arranged in rows between the muscle fibrillæ and in transverse lines in segment J on either side of the membrane of Krause. He also noted fatty fibers side by side with non-fatty areas. However, in other cases all the cells showed a uniform diffuse mottled appearance.

We do not wish to go into detail of the histology and chemistry of fats. Those interested can obtain in detail the reason for the conclusion of Bullard. Bullard gave decisive evidence for believing that visible droplets of neutral fat occur in physiological circumstances in the cardiac muscle fibers of mammals. Space prevents the repetition of these arguments and proof.

(He utilizes a 20 per cent. solution of formalin¹⁷ rendered isotonic with 0.75 gm. NaCl per 100 c.c. liquid. Tissues are fixed for one half to five hours and then cut on the freezing microtome. If this procedure is followed the quantity of fat does not differ from that obtained in fresh tissues. By means of Herxheimer's alkaline alcoholic solution of Scharlach R fat may often be demonstrated in larger amounts than by the simple alcoholic solution of dye. (This stain¹⁸ is a saturated solution of Scharlach R in 70 per cent. alcohol to which 2 gm. of NaOH are added to every 100 c.c. of fluid. Precipitates must be avoided.)

Within the last few years several articles¹⁹ have appeared in the literature that tend to prove that the pigment of brown atrophy is an endogenous melanin and that some of the red droplets in the cell brought out by the Scharlach R are of exogenous lipochrome. But this lipochrome is stained a deep blue by Nile Blue Stain, not red,¹⁵ as the fat granules are. Other writers too, state that the pigment can be separated from the fat.

The presence of fat in the cells of normal human cardiac tissue was not only a revelation to us but to others. An eminent pathologist was shown our Scharlach R sections of normal hearts. Without knowing the history of the cases he stated that the hearts were pathological, *i.e.*, that they were in the condition of fatty degeneration. He was surprised indeed to learn that the sections were from normal human hearts.

It must be clear by this time that visible fat is a normal finding in human cardiac muscle. Similarly it must also be evident that visible fat within the muscle cell does not signify fatty degeneration.

Although we believe that fatty degeneration is quite rare in hearts of those dying from cardiac disease, localized areas of fatty degeneration in the heart muscle are not so uncommon. One of our twelve pathological hearts depicted this finding. (See figure.)

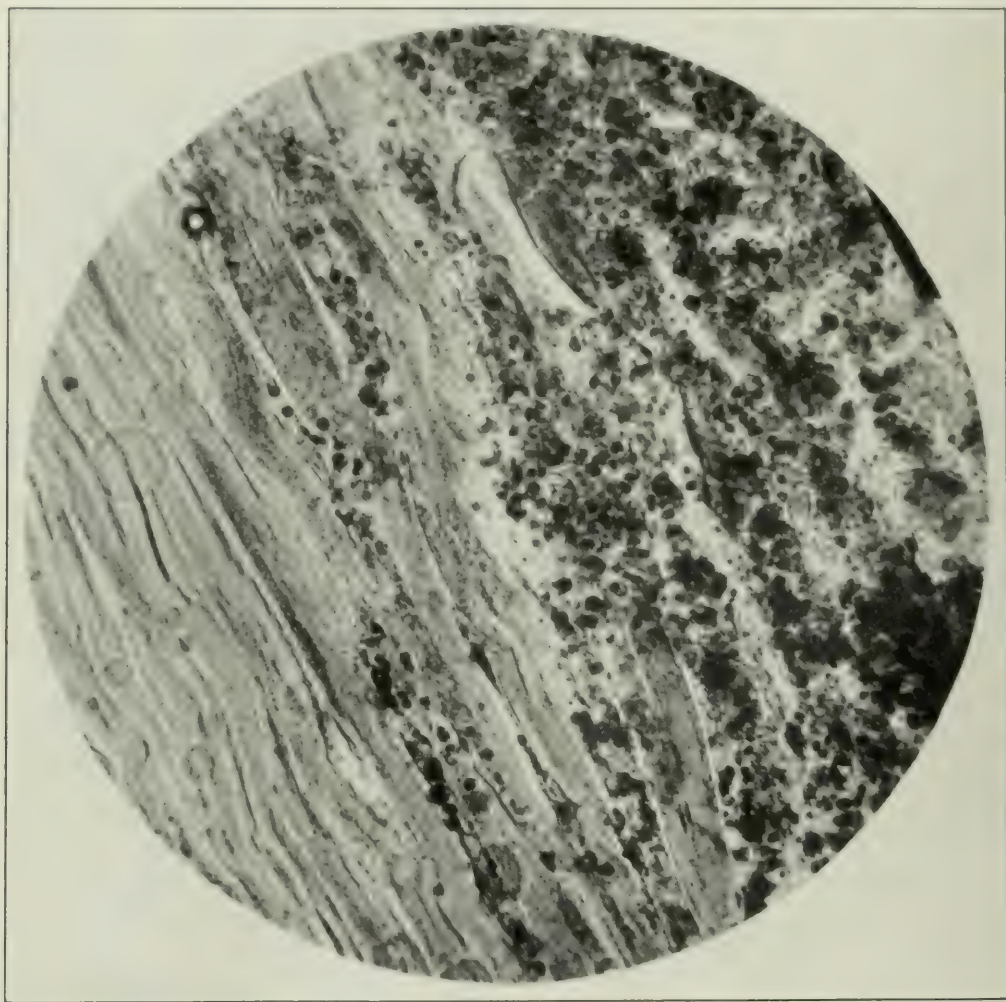


FIG. 4. Case A. Localized area of fatty degeneration in vicinity of infarcted heart muscle (low power microphotograph).

CASE 2. G. Coronary artery disease. The patient, 59 years of age, was admitted to the New York Hospital on May 25, 1921, and died June 7, 1921.

Sixteen months before entering the hospital the patient had a severe attack of abdominal gas pains. These recurred with increasing frequency with dyspnoea on exertion. Cough was present June 3, 1921. The pulse became irregular. The heart was enlarged slightly, and the sounds were distant. Clinically and from the electrocardiographic point of view the patient was considered to have coronary artery disease with thrombus formation. The blood pressure was systolic 110, and diastolic 70. The urine was normal. The Wassermann reaction was negative.

Gross examination of the heart showed that the organ was enlarged, weighing 500 gm. On the posterior surface of the left ventricle there was a pale focus. Three to four mm. beneath the endocardium there was a grayish yellow layer. The coronaries showed marked thickening; the lumen of the anterior descending branch of the left coronary was occluded by an old thrombus.

The microscopical examination revealed necrotic areas in the septum. Adjacent portions showed marked fatty degeneration as shown in sections stained with Scharlach R. There were areas of fibrous tissue replacement. In the lateral wall of the left ventricle there were also areas of fibrous replacement with less marked but very evident fatty degeneration and infiltration. The right ventricle appeared normal except for a slight increase of connective tissue. Here evidence of necrosis, fibrosis, nuclear changes, disappearance of muscle striations, great numbers of fat granules, etc., helped make the diagnosis of fatty degeneration of this localized area.

It appears therefore that in twelve hearts in which one might have diagnosed fatty degeneration of more or less severity not one showed this condition. This we proved on the basis of the normal hearts as a standard.

Certain facts must clearly be evident by this time: normal hearts contain microscopically visible fat; microscopically visible fat alone does not stamp a heart as demonstrating fatty degeneration; that fatty degeneration of the heart is much less common than supposed; that, clinically, fatty degeneration of the heart is therefore a very uncertain diagnosis.

SUMMARY

1. The clinical diagnosis of fatty degeneration of the heart is still made too commonly. It is a very uncertain diagnosis.

2. There are no symptoms peculiar to this condition, nor is there any pathognomonic sign for its diagnosis.

3. The diagnosis should be made by inference only. The etiological factors in fatty degeneration will help.

4. In reference to degenerative changes in the heart muscle, fatty and fibrous changes should not be differentiated clinically. This is Sir James Mackenzie's²⁰ view.

5. Fatty degeneration of the heart is a finding too frequently made post-mortem. The presence of microscopically visible fat in the muscle cell is not sufficient for this diagnosis.

6. In human cardiac muscle microscopically visible fat is normally present; it is by no means necessarily pathological. The fat resides in the sarcoplasm between the muscle fibrils and is arranged in longitudinal and transverse rows. Apparently the amount has no relation to the state of nutrition at the time of death; neither has the age of the individual (eight to fifty-six years), the color, nor the sex.

7. The picture presented by the diffuse red droplets (Scharlach R) or the black granules (osmic acid) closely resembles the classical illustrations that many of the textbooks of pathology utilize to picture fatty degeneration of the heart. True fatty degeneration, *e.g.*, the "tiger-heart," is recognized by the greater number and size of the granules, the evidences of inflammation, *e.g.*, nuclear changes, disappearance of striations, etc.

8. In all experimental work in which sections of cardiac tissue are stained for fat, normal conditions should be kept in mind and control performed whenever possible. In the investigation of twelve pathological hearts we found not one organ demonstrating fatty degeneration. Another writer performing work similar to ours reported "marked fatty degeneration" in every case.

9. The so-called pigment of brown atrophy of the heart, which is supposed to be an indication of degenerative processes, *e.g.*, senility, was found in moderate amounts in two healthy boys, one eight years old, the other fifteen.

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Discussion:

DR. ROHDENBURG: I think that Dr. Master is to be congratulated on his work. I can bear out one thing he speaks of. I have observed the localized fatty degenerations in a goodly number of cases associated with bundle branch lesions, where there had been a degeneration of the muscle fiber with large drops of fat and replacement fibrosis at the edge of the area of fatty degeneration.

DR. MACNEAL: I should like to ask if Dr. Master feels that the diagnosis of fatty degeneration should be made post-mortem in any case in which there is merely the presence of fat in the cells, or whether one should also have the fibrous replacement to justify such diagnosis at the present time.

DR. MASTER: In my work I only studied the ordinary cardiac muscle, and not the specialized tissue. In regard to the question of Dr. MacNeal, that is one of the points I am making, that you cannot diagnose fatty degeneration by the mere presence of fat in the cells. You must have all the other signs to do it.

CARCINOMA OF THE APPENDIX

ROBERT C. SCHLEUSSNER, M.D.

(From the Pathological Laboratory, Misericordia Hospital, New York City)

Since it has become customary to examine histologically all appendices removed at operation, carcinomas of the appendix have been frequently reported. It is estimated that 0.5 per cent. of all appendices removed are carcinomatous.

The specimen that I am presenting is therefore interesting only because it raises the question of the actual malignancy of the tumor. Batzdorf collected 186 cases and found that 6 per cent. were characterized by recurrences or metastases. But in this compilation are grouped both the common spheroidal celled carcinoma and the rarer true adenocarcinoma. Rolleston drew attention to the fact that these are two distinct groups and later writers on the whole confirm his view. The evidence that the typical adenocarcinomas are highly malignant seems quite conclusive (see Neugebauer; Voekler). The malignancy of the common spheroidal celled carcinoma is still a matter of debate, only one case having been reported as definitely malignant (Lejars). Some writers indeed consider these tumors to be endotheliomas and do not believe that they are ever malignant (Neugebauer).

Using McWilliams' and Rolleston's compilation of cases I looked up the original articles in those cases where the tumor (including adenocarcinoma and spheroidal celled carcinoma) exhibited malignancy either clinically or histologically. McWilliams found three cases (reported by Baldauf, Hartman, Lejars) and Rolleston four cases (reported by Beger, Ruyter, A. O. Kelly, Elting). I have abstracted the various case reports below.

CASE I. Baldauf. Patient was a male, aged 38, operated upon under the diagnosis of acute appendicitis. An appendectomy was done. Examination of the specimen revealed a portion of the appendix wall infiltrated by nests of oval or polygonal cells with considerable light cytoplasm and vesicular nuclei. The growth extended into the appendix mesentery. I believe that this fairly may be considered as a carcinoma of the spheroidal celled type. The patient made an uneventful recovery and there is no further note as to

subsequent history. The only evidence indicating malignancy in this case is the invasion of the mesoappendix.

CASE 2. Hartman. Patient was a woman, aged 29, operated on under the diagnosis of acute appendicitis. At operation several nodules were felt in the mesoappendix. A portion of the cecum at its junction with the appendix was removed along with the appendix. The patient made an uneventful recovery and was seen again after four years. At this time she was well and no masses were palpable in the right iliac fossa. Examination of the specimen removed at operation showed a nodule involving the base of the appendix and also a similar one distal to it. The mesoappendix also showed two nodules. Section showed all of these nodules to be carcinomatous infiltrations of the tissue involved. The wall of the cecum was also found to be infiltrated by the growth. The tumor was classified as an atypical adenocarcinoma. This patient then with a histologically malignant (*i.e.*, invasive) growth was well four years after operation.

CASE 3. Lejars. Patient was a male, aged 27. He was operated upon under the diagnosis of chronic appendicitis and an appendectomy was done. No gross tumor was found at operation but it was noted that the appendix was as large as a middle finger and that it had a peculiar pale whitish color. The mesoappendix and cecum were normal and no enlarged glands were felt. The wound healed but in two and a half months the patient returned with a marked cachexia, a large mass in the right iliac fossa and flank, ascites, enlarged left supraclavicular glands and a subcutaneous tumor in the abdominal wall just to the left of the umbilicus. A laparotomy was done and a large mass was found involving the cecum and ascending colon and extending into the mesentery. A portion of the subcutaneous tumor to the left of the umbilicus was removed.

The appendix showed an epithelioma consisting of polygonal cells arranged in trabeculae and involving all layers of the appendix. Apparently the mesoappendix was not involved. The subcutaneous nodule removed at the second operation showed a histological picture identical with that found in the appendix.

CASE 4. Beger. Patient was a male, aged 47, who exhibited an ulcerating mass involving the skin in the right iliac fossa. At operation the mass was found to extend down to and involve the appendix, but also the cecum at the ceco-appendicular junction. Histologically it was a typical adenocarcinoma with cylindrical and goblet cells lining the lumina of the tubules. The evident involvement of the cecum at the time of operation casts doubt upon the primary origin of the tumor. The patient died a few hours after operation. At autopsy the retroperitoneal glands were found to contain metastases.

CASE 5. Ruyter. The patient was operated upon for appendicitis. Several years later he was readmitted to the hospital with a leg infection and a pyemia from which he died. At autopsy a small cystic tumor of the appendix stump was found. This turned out to be a colloid carcinoma on microscopic examination. There is no report of any examination of the appendix at the time of its removal. The author mentions this case among several carcinomas

of various types which had appeared in inflammatory tissue. There is nothing to prove that this tumor was a recurrent one.

CASE 6. A. O. Kelly. Case 4 cited by this author was a male, aged 63, who was operated upon because of recurring attacks of pain in the right iliac fossa. At operation it was noted that the appendix and intestines were studded with numerous grayish-white nodules like tubercles. An appendectomy was done. Examination of the appendix showed the wall replaced throughout by nests of epithelial cells varying much in size and shape. While solid alveoli of cells seemed to predominate, some hollow cylindrical arrangements lined by a single layer of epithelial cells were to be found. The presence of goblet cells is not mentioned. The mesoappendix was involved by the tumor. This patient died of shock one week after the primary operation as a result of secondary suture of the wound which had broken down.

CASE 7. Elting. This case was one in which appendix, cecum, ascending and transverse colon, and ileum were involved in a colloid carcinoma which seemed to have started in the appendix. Again, here, its origin must remain doubtful because of the extensive involvement when the tumor was first discovered.

Of these seven cases only four (Baldauf's, Hartman's, Lejars', and Kelly's) seem to be certain primary carcinomas of the appendix. The descriptions of the histological pictures presented in these various cases do not allow one definitely to group these cases together, but on the whole they would seem to belong to the group of spheroidal celled carcinomas. Granting that they belong to this group, which is the group to which the great majority of appendix carcinomas belong, it will be seen that there is definite clinical indication of malignancy in but one case (Lejars'). The other three cases present some evidence of malignancy in that the tumor is histologically invasive, but the clinical evidence of malignancy (metastases or recurrence) is lacking.

Though Lejars' case has been carefully studied and reported, its great malignancy in contrast to the other cases reported stands out so prominently that one thinks of a possible error of observation.

The case that I have to report is that of a woman aged 41 who was operated upon March 3, 1922, by Dr. Marton at the Misericordia Hospital.

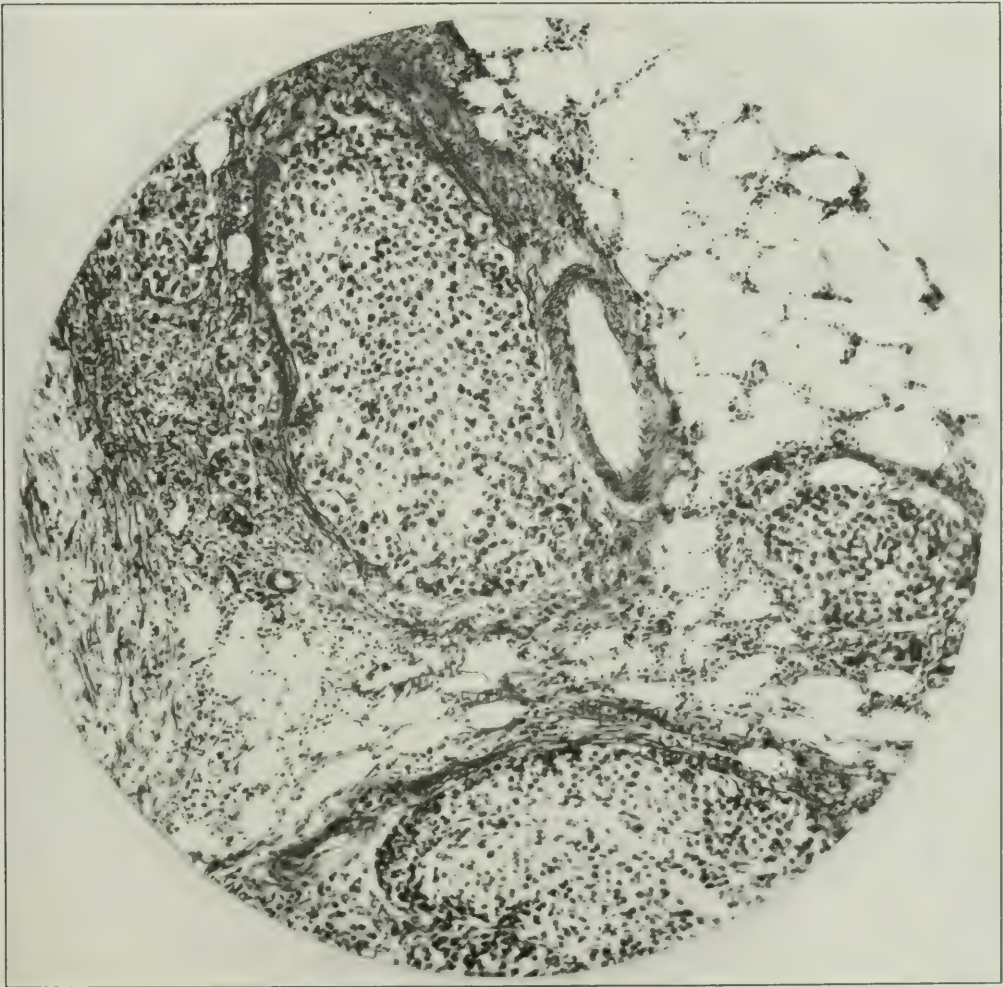
Family and past history were negative.

Present illness: She always enjoyed good health until last summer (six or eight months ago) when she began to complain of backache. Three weeks ago she was seized with severe abdominal pain. Pulse and temperature were normal at this time. She vomited but once a few days prior to operation.

Operation: On examining the patient under ether it was found that Douglas' cul-de-sac was tense and a posterior colpotomy was done because of the belief that a pelvic abscess was present. No pus was found and a laparotomy was then undertaken. An appendix abscess was found. The appendix was but lightly adherent to the adjoining viscera and was easily removed. The pelvic viscera were normal and no evident mesenteric or retroperitoneal glandular enlargements were noted.

The patient had a stormy recovery. At first she did poorly but now (three months post-operative) she is steadily improving.

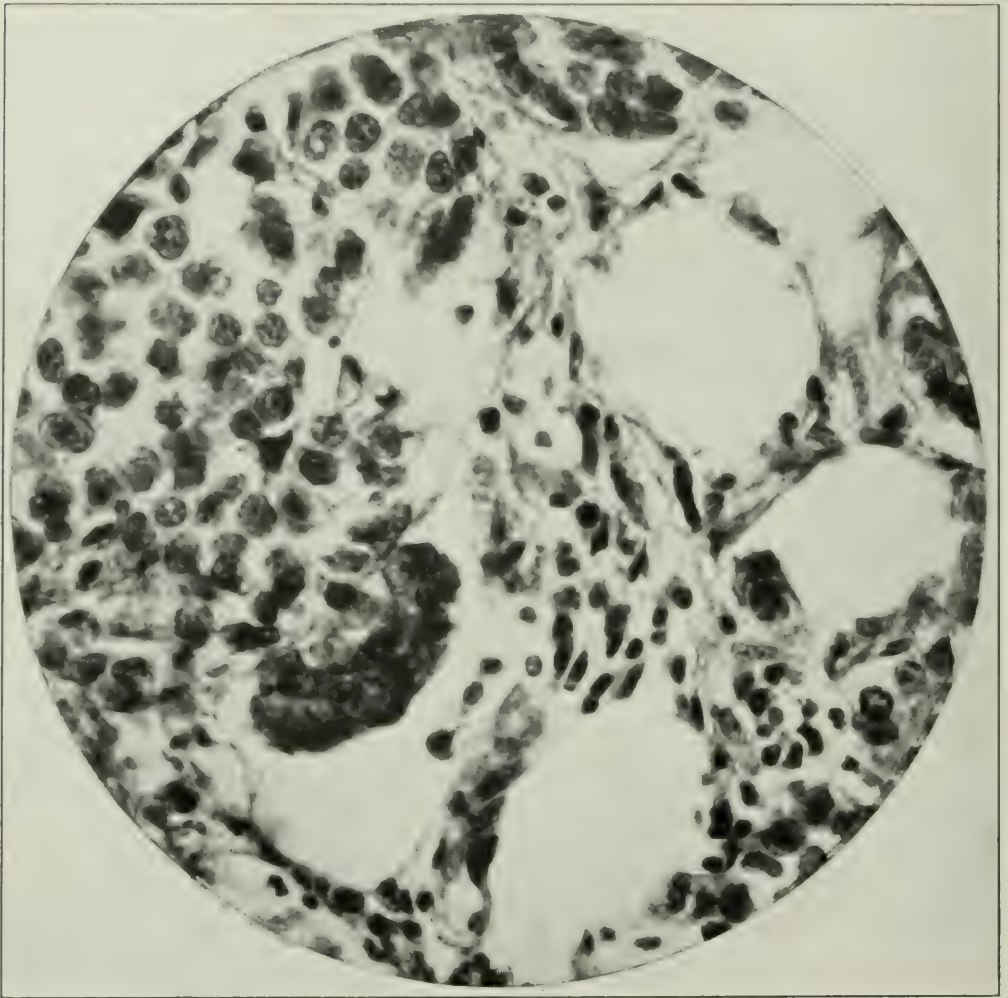
Pathological report: Gross examination of the specimen reveals an appendix measuring 6 cm. in length. Its proximal half measures 8 or 9 mm. in diameter, while the distal half measures about 12 mm. in diameter. The serosa is congested and shows slight roughening in small areas. Section through the wall at the proximal portion reveals the lumen filled in by a firm white tissue appearing in the gross like connective tissue. Section through



Photomicrograph of nodules in mesentery of appendix. $\times 150$. (Made by Crocker Research Laboratory.)

the distal half of the appendix reveals a different picture. Here the lumen is filled in by a uniform grayish-yellow tissue quite different from anything found in the usual appendix. Moreover the adjoining portions of the meso-appendix are closely studded by nodules of a similar appearance.

Microscopic examination: Sections taken through the distal half of the appendix reveal the central yellowish tissue to consist of large alveoli of epithelial cells. The individual cell is of moderate size, polygonal, shows a pale slightly eosinophilic cytoplasm and a large round nucleus, moderately rich in chromatin. Occasional mitotic figures are encountered. The serosa, muscularis and submucosa are all extensively infiltrated by similar alveoli of cells and the mesoappendix shows a similar invasion. The cell nests seem in some places to occupy lymph sinuses, but in other places they lie outside of these channels. The epithelial cells are sharply set off from the surrounding tissue. There is no suggestion of gland formation and no goblet cells are seen. The central cells of some of the alveoli show necrosis. Nowhere can blood



Photomicrograph showing invasion of mesentery with tumor cells growing in lymph sinuses. $\times 400$. (Made by Crocker Research Laboratory.)

vessels containing tumor emboli be seen. The connective tissue between the alveoli shows a moderate cellular infiltration consisting mostly of lymphocytes though polymorphonuclear leucocytes and plasma cells are also to be found. Here and there isolated tumor cells are to be found.

Sections taken through the base of the appendix show complete absence of tumor invasion either of the appendix itself or of the adjoining mesoappendix. The serosa is edematous and congested and shows a slight fibrosis. It exhibits a profuse cellular infiltration consisting of lymphocytes and polymorphonuclear leucocytes in about equal numbers. The mucosa has disappeared and the lumen is filled in by young connective tissue showing, especially toward the center, a profuse lymphocytic infiltration. A few neutrophile and eosinophile leucocytes are present. The small blood vessels throughout the section show accumulations of polymorphonuclear leucocytes.

Diagnosis: Subacute inflammation of an appendix exhibiting a spheroidal celled carcinoma with involvement of the mesoappendix.

SUMMARY

1. This paper is based on the premise that spheroidal celled carcinoma and adenocarcinoma of the appendix are different entities from a histopathological standpoint.

2. The malignancy of the adenocarcinoma is admitted.

3. Attention is called to the fact that but one case of the numerous spheroidal celled carcinoma reported has exhibited clinical malignancy, and the need of further reports to confirm the potential malignancy of this tumor is pointed out.

4. A spheroidal celled carcinoma of the appendix with involvement of the mesentery is reported.

In concluding, I wish to thank Dr. Marton for his courtesy in furnishing me with the clinical details of this case.

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The articles of Kudo and McWilliams have extensive references appended to them.

Discussion:

DR. VANCE: I have been very much interested in the question of carcinoma of the appendix. This type of carcinoma is very similar to a group of tumors which was described some years ago before this Society; they were tumors of the small intestine which had exactly the same histological appearance as this, and to a great extent the same type of growth—a very slight infiltrative growth into the lymphatic vessels. It is interesting to note the report of the infrequent malignancy. A few months ago I had occasion to find a tumor of the intestine in a man forty-eight years old who was killed by a fracture of the skull, and this tumor histologically was of the same type as the carcinoma of the appendix, but it had metastasized to the liver and lymph nodes. To judge by the pathological condition of the body, the tumor had had no effect on the health of the patient. Death was entirely due to the accident, but it is very interesting that the tumor had the same arrangement in trabeculæ and cubical cells as in the carcinoma of the appendix.

DR. MEEKER: I wish to state that two months ago at the New York Post-Graduate Laboratory we had a series of nine appendices showing primary tumors of the type reported tonight by Dr. Schleussner, and of these only one had extended into the mesentery. They occurred between November 8th and January 20th, and the total number of appendices received during that time was 200, making the percentage of these tumors 4.5 per cent. for that period.

FINAL REPORT

Since the above article was written the case reported has come to a fatal termination in a manner which leaves little doubt that the tumor in question recurred and metastasized, even though no autopsy could be obtained. Dr. Marton, who observed the case from beginning to termination, has been kind enough to furnish the following data:

Patient was discharged April 11, 1922, after a stormy convalescence. Thereafter she gained weight; her appetite improved and she lost the cachectic appearance she had had just after operation. On June 14th she began to bleed freely from the vagina. Examination at this time showed the bleeding to

come from a broken-down area in the posterior vaginal fornix at the site where a drain had been placed into the cul-de-sac at the time of operation. Patient continued to bleed intermittently from this area for six weeks and during this time nodular masses appeared throughout her abdomen. These increased rapidly in size and the patient became increasingly cachectic. She died August 17, 1922.

The rapid course of the disease (clinical recurrence in three and one half months and death in five and one half months) corresponds with the course of the fatal case reported by Lejars.

The report of Lejars regarding the potential malignancy of the spheroidal-celled carcinoma of the appendix has herewith received its first corroboration in the literature in the sense that here again a case is reported that has exhibited a high degree of clinical malignancy.

THREE RAPIDLY FATAL CASES OF TRICHINOSIS WITH AUTOPSY REPORTS

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and*

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The following report is a brief summary of three fatal cases of trichinosis, all occurring in the same family.

The probable source of infection was a meal of pork chops, eaten on November 11, 1921. At various intervals thereafter seven members of the family became ill, of whom three died in Broad Street Hospital. They were Margaret G., age eleven years, who died on November 28, 1921, about sixteen days after the probable date of infection; Mary G., age forty-nine years, date of death December 4, 1921, duration of disease about twenty-two days; and Joseph G., age eight years, date of death December 5, 1921, duration of disease twenty-three days.

The clinical histories of these cases will be described fully in another place. It is sufficient here to point out merely the rapidly fatal course of the illness. The fatal cases were autopsied by the Medical Examiner's Office, all within thirty hours after death.

Margaret, aged eleven, poorly developed and nourished, had œdema of the subcutaneous tissue in the lumbar region, and the legs appeared slightly puffy. Aside from injection of the meninges of the brain and spinal cord and the vessels of the brain itself, the viscera were practically normal.

Mary, aged forty-nine, slightly obese, presented negative findings except for the brain. The vessels of the dura, pia and brain were markedly injected. In the right frontal lobe were pinhead-sized hemorrhages, grouped in an area measuring several centimeters in diameter in the white matter, and scattered in the gray matter.

Joseph, aged eight, was considerably emaciated and the skin and mucous membranes were pale. There was a large abscess in and under the left pectoral muscle. The lungs showed early peribronchial infiltration. The right middle ear contained pus. There was a moderate excess of cerebrospinal fluid, which appeared rather turbid, and the blood vessels of the meninges of the brain were markedly injected. *Streptococcus hemolyticus* was cultured from the spleen. These pathological findings were interpreted as manifestations of streptococcus sepsis, the focus being the abscess in the left pectoral muscle.

None of the cases showed intestinal lesions nor any abnormal character of the intestinal contents.

Microscopic examination of these three cases showed practically identical lesions with a few minor differences. There was marked myositis in all the skeletal muscles examined, consisting of local infiltration of many polynuclear eosinophile leucocytes, lymphocytes, a few neutrophile leucocytes, and other inflammatory cells; in most cases these cells were grouped around the smaller blood vessels and between the muscle bundles.

Trichinæ were found in the muscle fibres in all three cases. The individual fibre involved showed atrophy and, in advanced cases, the formation of characteristic large cubical cells surrounding the worm, considered by many to be myogenic in origin and inflammatory in nature.

The grade of the process and the stage of development of the worm varied in different cases. In the little girl who died about two weeks after infection, some of the worms were forty times as long, others twenty times as long, as the red blood cell. Similar worms were present in the boy, who died after an illness of three weeks' duration, and they were especially evident in the abscess of the left pectoral muscle. Only one worm was found in the diaphragm of the woman, who lived about three weeks after infection. This embryo was about twelve times as long as a red blood cell, and was obviously a very early stage in the development of the worm. In all the muscles the trichinæ were extended, straight, or only slightly curved; none were coiled in a spiral or encapsulated.

The heart muscle showed some myositis, rather marked in the case of the little girl, where the areas of cellular infiltration involved much of the myocardium proper. In the woman and boy, however, there was only a mild grade of the process, confined to the heart muscle near the pericardial surface. No trichinæ were found in the heart muscle.

Sections of the brain and cord of the girl were negative. There was a

perivascular lymphocytic infiltration around some of the arteries in the brain substance, in the case of the boy. The woman, however, showed marked meningitis and hemorrhagic encephalitis. The vessels of the cerebral cortex were plugged by fibrinous thrombi and the sub-arachnoid space was infiltrated by large epithelioid and other inflammatory cells. The area of encephalitis showed marked perivascular hemorrhage, but scarcely any cellular response. There were plugs of ovoid outline in some of the finer blood vessels in this region, but it was impossible to identify them as parts of the trichina embryo. However, it is reasonable to conclude that the trichinosis was responsible in some way for the meningitis and encephalitis. The intestine of the boy was sectioned, but nothing abnormal was found.

The other viscera showed nothing of significance.

The interesting features of these three cases are, first, the rapid and fatal course of the disease, reckoning from the probable date of infection; second, the different sizes and stages of development of the intramuscular trichina embryos. According to Staubli, postmortem examinations on cases that have a clinical course of less than three weeks are almost unknown or, at least, quite rare. The girl died in slightly over two weeks' time, while the woman and boy succumbed a week later. The fact that two of the deceased were children appears to be a rather unusual feature, as the disease is supposed to run a much milder course in children than in adults.

The differences in size and the general lack of coiling of the various intramuscular embryos indicate a recent infection and also a discharge of trichina embryos into the intestinal lymphatic circulation in successive intervals. This is quite in keeping with the life history of the adult trichina forms, as it has been observed in the intestinal tract.

The meningeal and brain lesions in the case of the woman are extraordinary, but have been described before by Frothingham and others. The muscular lesions, however, are typical of the disease, though the process is, perhaps, a little more acute than is ordinarily seen in sections of skeletal muscles removed at biopsy and autopsy.

Discussion:

DR. MACNEAL: I should like to ask if you had a large amount of muscle tissue preserved from each case. I understand this was an accidental finding made when the tissues were examined microscopically.

DR. VANCE: We saved as many muscles as we could.

DR. MACNEAL: Did you save any of the extra-ocular muscles?

DR. VANCE: No, we only saved those of the neck, of the larynx, and of the diaphragm.

A CASE OF ACUTE LYMPHATIC LEUKEMIA

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The present case is presented not because the condition described is novel but because the opportunity was offered of a thorough observation and of applying all of the usual methods of treatment.

The patient, a young girl aged eighteen, had an uneventful past and family history. Five weeks before the onset of the disease which caused her death, she was immunized in the usual fashion against typhoid fever, the vaccine used being a sensitized preparation. At the conclusion of this immunization she went to a girls' camp for the summer. After being in camp about ten days ecchymoses appeared on the face and extremities and menstruation, which was then present, became very profuse and continuous. At the same time a temperature was present. She came under our observation five days after the onset of these symptoms.

Her parents had noted that in the previous spring she had been rather pale and had tired more easily than before. Physical examination showed an exceptionally well-developed muscular girl, whose general appearance indicated an acute anemia. The only positive physical findings were: a spleen enlarged so as to reach almost the median line of the abdomen, palpable glands in the axillæ and neck, and a metorrhagia of profuse character. The results of laboratory investigations were negative except for the changes in the blood presented in the accompanying table.

The bleeding from the uterus keeping up and the clinical diagnosis of an acute lymphatic leukemia being made, a transfusion was done on the tenth day and again on the twelfth day of the illness. Between the two transfusions radium was applied to both ovaries. The total white count had commenced to fall before the first transfusion and on the thirteenth day of the disease was 400 as compared with 44,000 on the second day of the disease. On the seventeenth day a third transfusion was given and in the interval between the second and third transfusion two injections of 0.1 gm. of silver-arsphenamine were given. During this period the uterine bleeding had diminished considerably but had not stopped. In order to completely control the bleeding the uterus was treated with a copper electrode and the galvanic current. The leukopenia continued, though the differential count showed a gradual recession of the lymphocytes. The hemoglobin and red cells gradually increased and

TABLE

Day of Disease	Total Leucocytes	Lymphocytes		Hemoglobin	Red Blood Cells	Remarks
		Small	Large			
2	44,000	73	65	3,560,000	
5	5,400	49	40	76	3,400,000	Platelets 250,000
6	20,700	84	12	72	3,200,000	
7	23,000	88	8	60	2,600,000	
8	9,800	98	50	1,800,000	
9	Transfusion, 540 c.c.
10	400	100	36	2,230,000	Radium, 100 mg., 12 hours, to ovaries
11	Transfusion, 800 c.c.
12	400	79	21	49	1,900,000	
13	1,000	88	12	47	2,100,000	Silver salvarsan, 0.1 gm.
14	400	80	20	38	1,500,000	
15	700	98	38	1,650,000	Silver salvarsan, 0.1 gm.
16	Transfusion, 800 c.c.
17	700	98	49	2,144,000	
18	1,000	70	51	2,384,000	
19	1,200	68	48	2,380,000	
20	800	70	48	2,496,000	
21	700	68	42	1,840,000	Silver salvarsan, 0.1 gm.
22	800	72	45	1,980,000	Radium, 100 mg., 12 hours, to spleen
23	Transfusion, 320 c.c.
24	800	44	50	2,128,000	
25	800	23	50	2,248,000	
26	1,500	33	60	2,544,000	
27	1,400	44	55	2,460,000	
28	1,800	42	55	2,400,000	Silver salvarsan, 0.1 gm.
29	2,000	32	53	2,722,000	Nucleated red cells
30	2,000	23	45	1,820,000	" " "
31	2,700	24	45	1,960,000	
32	2,600	24	48	2,230,000	Nucleated red cells
33	3,200	16	40	1,800,000	
34	3,200	26	43	2,240,000	
35	Transfusion, 530 c.c.
36	4,600	15	54	2,880,000	
37	3,800	14	52	2,700,000	
39	4,800	20	64	2,240,000	
41	6,000	20	72	2,800,000	
43	12,000	24	81	3,700,000	
46	9,800	17	89	4,200,000	
50	99,600	38	102	4,330,000	
51	124,000	50	95	4,224,000	6 per cent. myelocytes
						Radium, 100 mg. 12 hours, to spleen
52	97,000	55	96	4,340,000	
53	80,600	56	100	4,460,000	
54	72,400	64	96	4,320,000	
55	182,400	86	80	4,768,000	

the temperature still continued. A fourth transfusion was given on the twenty-fourth day and a fifth on the thirty-eighth day of the disease, injections of silver arsphenamine and radium applications being continued between the transfusions as indicated in the table. During this period the temperature receded, the total white count gradually rose to 3,200; the differential count approached the normal, while the red cells and hemoglobin remained about the same. The spleen in the meantime returned to its normal size, the glands were no longer palpable and for several days there was a normal temperature.

It was thought at first that we were dealing not with a true leukemia, but with one of those leukemic-like reactions which others, notably Cabot, have described and which we have twice encountered, once during a pneumonia and again in the course of an intestinal infection of unknown etiology. Unfortunately however five days before death the picture quite suddenly changed; the total white count rapidly rose to 182,000 and the differential count again assumed the characteristics of leukemia, though the hemoglobin and red cells remained high. Two days before death a few ecchymoses appeared on the cheek, and the post-auricular and axillary glands again became enlarged. The spleen remained small until the day before death when it increased in size from hour to hour with almost unbelievable rapidity, changing in less than fourteen hours from a nonpalpable size until the edge was palpable across the median line. Death occurred with a cardiac collapse.

The case is presented as one of acute leukemia during which there occurred a phase of leukopenia followed by an almost complete return to the normal and then a recrudescence of the leukemic phase. Though the initial impression was one of therapeutic success, the final outcome conclusively showed the erroneous nature of this impression.

Discussion:

DR. ROSENTHAL: I would like to inquire was it the radium that did all this. We know that radium is detrimental to the bone marrow and blood cells, and it is a question whether the marked destruction of the bone marrow produced the marked diminution of the cells at first, and later on there was a sudden increase and outpouring of the cells which were previously inhibited.

DR. DARLINGTON: At the fiftieth day had the physical condition improved?

DR. ROHDENBURG: The decline in the leucocyte count had occurred before radium was applied and before the first transfusion had been given. On the morning of the day the radium was applied the leucocytes were around 1,000; they ran between 400, 800, and 1,500 for nearly two weeks. The decrease in cells I do not think can be attributed to the radium.

On the fiftieth day the physical condition was such that all preparations were made to take her to the country. Her father had gone to one of the Jersey coast resorts, and while he was gone she developed a few ecchymotic

spots on her cheek. The spleen had enlarged for the second time until eighteen hours before death, when it increased in size from hour to hour. This sudden increase in size caused excruciating pain.

MULTIPLE THROMBOSIS WITH POLYPOID THROMBUS IN THE RIGHT HEART

W. A. CHIPMAN, M.D.

(From the Pathological Laboratory, Bellevue Hospital, Dr. Douglas Symmers, Director)

Cardiac thrombi, exclusive of the vegetation of acute valvulitis, are of two types, namely, globular and polypoid thrombi. Globular thrombi are much the more common of these two types. They vary in size from that of a pea to that of a hen's egg. They present a number of characteristics, such as multiplicity, with adjacent thrombi often connected by a fine meshwork, broad or sessile attachments, bland softening of the central portion with the peripheral portion remaining as a thin shell which rarely bursts, and degeneration of the underlying myocardium. This type of thrombus rarely undergoes organization.

Cardiac polypoid thrombi are a relatively rare pathologic entity. In Welch's series of 33 authentic cases, 25 sprang from the wall of the left auricle, usually the septum, 4 from the left ventricle, and 4 from the right auricle. From the time his paper was published (1899) to the present writing, no additional cases are listed in either the Quarterly Cumulative Index or Index Medicus, unless certain of the cases reported as myxomata are in reality organized thrombi.

Cardiac polypoid thrombi present a number of noticeable features. There is no discernible cause for their occurrence in many instances, the hearts containing them being normal except for changes secondary to the thrombus. They are solitary formations rarely occurring with other thrombi. From the above statistics, it is seen that most of these thrombi occur in the left auricle. They are usually attached at the fossa ovalis by a short pedicle and simulate true cardiac tumors, being firm or gelatinous.

ovoid in shape, usually with a smooth glistening surface, not unlike endocardium. These growths may show calcified, pigmented or atheromatous patches. The color varies from a yellowish fat-like substance to brownish red. Differing from all other cardiac thrombi, these polypoid growths are usually organized, the process often being so advanced as to simulate a myxoma or fibroma. In those less organized, the thrombus consists of red cells, granular detritus, leucocytes, pigment, fibrin and occasional connective tissue cells, together with newly formed blood vessels.

Three theories have been advanced to account for the origin of these polypoid thrombi, namely, thrombosed varices (Bostroem), hemorrhage into the septal wall (Bostroem), and degeneration of the myocardium (Krumm). Bostroem cites four cases: two representing thrombosed varices, the third that of a ball thrombus which had recently broken from its septal attachment and was histologically a thrombosed varix, and the fourth that of a polypoid thrombus with hemorrhage into the septal wall as the etiological factor. On the other hand, Krumm cites one case in which there was localized disease of the heart wall.

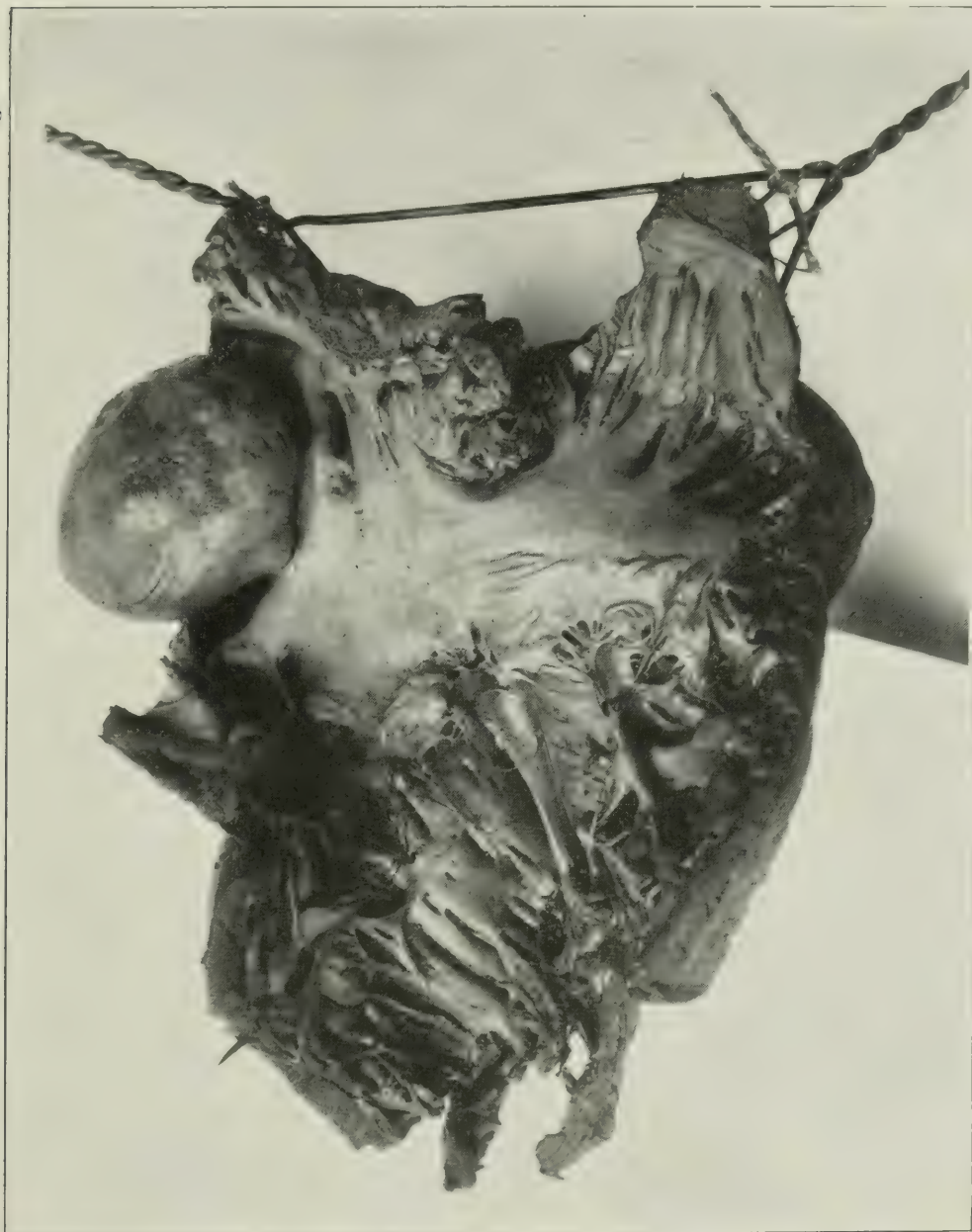
There is considerable dissension, especially among the German writers, as to whether "tumors" arising for the most part from the fossa ovalis of the septum of the left auricle should be classed as polypoid thrombi or as myxomata, or whether both exist. The type of tumor classified as a myxoma is gelatinous, yellowish to brownish red, polypoid or oval in shape, sessile, with a narrow or broad pedicle, and has a glistening smooth surface, not unlike endocardium. Histologically, they have a matrix much like Wharton's jelly, give a positive mucin reaction (mucicarmin "Mayer," mucihematin "Mayer," or thionin "Hoyer") and have newly formed blood vessels. Thorel considers most of these to be organized thrombi, whereas Ribbert maintains they are true tumors.

The case to be reported presented the following history:

The patient, a white man 60 years of age, was admitted to the service of Dr. Theodore Abbott, Bellevue Hospital, on April 10, 1922, and died six days later. On admission, he complained of dyspnoea and edema of the eyelids and feet. In addition to the dyspnoea and edema, which had been present to a

minor degree for six or seven years, he complained of cough, with blood-streaked sputum, for two months prior to admission.

Physical Examination: Physical examination showed puffiness about both eyes, unequal pupils which failed to react to light but reacted sluggishly to accommodation, moderate albuminuric retinitis, and chronic conjunctivitis. There were abnormal venous pulsations in the neck. The heart was enlarged,



fibrillating, with a pulse deficit of about sixteen beats to the minute, with a double murmur at the base transmitted down the left side of the sternum, and a systolic murmur at the apex. There were signs of pneumonia in the right

upper chest. The liver was palpable, but neither pulsating nor tender. There was questionable ascites, with edema of the lower extremities, extending to the knees.

Urinalysis showed albumin in rather large amounts, a specific gravity of 1.020, hyaline and granular casts and blood cells. The phenolsulphonephthalein test was 25 per cent. in the first hour, and 30 per cent. in the second hour, and the blood chemistry showed a non-protein nitrogen of 38.5 mg. and a creatinine of 1.3 mg. per 100 c.c. of blood. The blood pressure was 150 systolic, 85 diastolic.

Necropsy Findings: Inspection of the body revealed edema, otherwise nothing of note. On opening the abdomen, there were about 200 c.c. of fluid in the peritoneal cavity. There likewise appeared to be fluid in both pleural sacs and in the pericardial sac (chest opened via diaphragm). The heart was large with a dilated right auricle. On opening the right auricle, there was a polypoid mass, 45 cm. in length by 3 cm. in diameter, attached by a short pedicle 1 cm. in diameter to the auricular septum at the fossa ovalis, and hanging down to partially occlude the tricuspid valve. It was soft, semi-fluctuant, yellowish, except at the base where it was brownish red. The surface was smooth, glistening and appeared to be covered by endocardium. In the auricular appendage there were several gray thrombi, measuring from 0.5 to 1.5 cm. in diameter. The tricuspid valve appeared normal. At the apex of the right ventricle, among the columnæ carneæ, was a gray thrombus, 1 cm. in length and half as wide. The mitral leaflets were thickened, but the opening admitted two fingers. The cusps of the aortic valve were fused for about 3 mm. The aorta, especially the arch, was roughened, somewhat wrinkled, thickened, but not calcified. **The coronary arteries were somewhat sclerotic.**

The upper and middle lobes of the right lung showed lobar pneumonia. There was a stellate "scar" of the pleura over the lower lobe of the left lung. The liver was of the nutmeg variety. The kidneys were normal in size, but otherwise presented the picture of chronic arteriosclerotic nephritis. The head and neck were not examined.

Anatomical Diagnosis: Heart—Multiple thrombi—right auricle and right ventricle, aortic stenosis, sclerosis of aorta and coronary vessels, hypertrophy and dilatation. Lungs—Organizing lobar pneumonia (right upper and middle lobes and left lower lobe), fibrous pleuritis (right), "syphilitic" scar of pleura. Kidneys—Chronic diffuse nephritis (arteriosclerotic). Liver—Chronic passive congestion with central necrosis. Petechial hemorrhages on inner side of elbow joint, chest and legs.

Histologic Findings: The heart showed moderate hypertrophy in general, with some hyperchromatosis of the nuclei throughout. There was little increase in fibrous tissue, except in sections near thrombi. Microscopic sections through the septum and polypoid thrombus showed hyperchromatic muscle nuclei, with swollen sarcoplasm. The polypoid thrombus consisted of fibrin with little cellular structure except for great numbers of newly formed blood vessels, and clusters of endothelial cells in which a lumen had not been formed. There was some lymphocytic infiltration about these cell cords. In one pole of the polypoid thrombus there was a large area of fresh hemorrhage, con-

sisting of well-preserved red corpuscles, through which coursed many newly formed and forming vessels. Scattered throughout there were small areas of blood pigment (old hemorrhage). At the site where the thrombus was attached to the auricular wall there was marked focal thickening of the endocardium from which a spur passed inward, separating the muscle bundles. This plaque consisted of relatively acellular, edematous, fibrous connective tissue in which were numerous capillaries. Scattered through this area there were numbers of rounded or oval structures, with small hyperchromatic nuclei, and with purplish, granular cytoplasm (degenerated muscle cells). Along the inner border of this area there was marked round-cell infiltration, especially marked about some of the vessels. The endocardium at a corresponding point on the opposite side of the septum showed similar changes. In places, this plaque merged imperceptibly with the polypoid thrombus, whereas, in other places, the line of demarcation was quite distinct. The endothelium of the auricle appeared to reflect onto the pedicle, and continue over the mass.

Microscopic examination of the auricular muscle and thrombi in the appendage showed marked degeneration of the muscle with indistinctly staining sarcoplasm containing vacuoles. The nuclei were swollen, either very pale or deeply hyperchromatic. The endothelium beneath the thrombi was destroyed. All the thrombi presented a similar histologic picture—collections of detritus through which were indistinctly formed granular columns, and, about the periphery, leucocytes, red cells and fibrin. The thrombus in the ventricle presented the same picture, except for beginning organization along the ventricular border. The muscle beneath the ventricular thrombus showed one or two focal areas of fibrous connective tissue in which there was round-cell infiltration.

Microscopic examination of the upper lobe of the right lung showed organizing pneumonia. Sections through the pleural "scar" of the left lower lobe showed marked thickening of the pleura, extensive perivascular round-cell infiltration, and marked endarteritis.

Examination of the kidneys showed advanced nephritis of the arteriosclerotic variety. The liver histologically showed chronic passive congestion with central necrosis. The spleen also showed chronic passive congestion.

Discussion:

DR. BISHOP: There is apparently a case of cardiorenal disease with fibrillation and paralysis of the auricle. This subject is highly important at the present time, because in the last two years quinidin sulphate has come into use. This drug apparently has the power of restoring contraction to some of these auricles which have been paralyzed for a long time, and about five per cent. of these old cases of fibrillation in degenerated hearts of just the type described here have shown embolism after the contraction of the auricle has been restored, so the existence of these thrombi clinically must be fairly frequent in these old cases. This makes it of doubtful good judgment to treat very old cases of fibrillation with quinidin. The important matter would be to have some criterion by which we could judge whether these auricles were

so affected before we had a chance to examine them pathologically, because testing them out by the quinidin treatment is a rather dangerous way of proving that thromboses do exist.

DR. MACNEAL: Was quinidin used in this case?

DR. CHIPMAN: He received tincture of digitalis, ℥ xx, every four hours, but no quinidin. Before death he received adrenalin, ℥ xv, every fifteen minutes for six doses with no benefit.

OSSIFICATION OF ARTERIES

LEILA CHARLTON KNOX, M.D.

Ossification as a phase of late stages of chronic inflammation and subsequent to calcification is not in certain organs a particularly rare lesion. In the choroid coat of the eye, for instance, it is found to follow 89 per cent. of the infections which are severe enough to cause loss of the organ; and small osseous deposits have been found in the lungs by Pollak and Lubarsch in about 70 per cent. of those which were the seat of chronic pulmonary infections, generally tuberculous. Almost every organ has been found ossified to a limited extent but so irregular is the process that it may scarcely ever be anticipated. In animals the reverse is true, and inflammatory lesions in rabbits, dogs, and birds readily ossify following comparatively slight trauma or short-lived infection. Illustrative of this are the experiments of Harvey who initiated the production of bone in the adventitia of the aortas of a series of rabbits by a single application of silver nitrate to the outer surface of the vessel; and the earlier work of Sacerdotti and Frattin who found bone in the kidneys of rabbits three months after the ligation of the renal artery. These experiments however shed little light on the cause of the process in human beings, nor are we able to understand upon what the difference in incidence depends. It cannot be explained as directly due to the calcium content of the blood for the differences between animals, and between man and animals, are so slight that no importance can be attached to them, the whole blood of rabbits, according to Abderhalden, containing 0.072 parts of calcium per 1,000, of dogs 0.055, while that of man contains from 0.090 to

0.110, these figures varying only slightly and in a few conditions.

But this is of course only one factor in a complex reaction. It is certain that all bone formation except in osteogenic tissue is preceded by calcification and that the precipitated salts are an essential to the production of the osteoid matrix and conversion of the fibroblasts of granulation tissue into osteoblasts and to the production of the marrow cells. The initial step in this process, the deposition of calcium, may take place in any tissue or organ, epithelial, connective tissue or endothelial, and is rather common in neoplasms. It is not dependent upon the age of the subject as calcification of portions of the cardiac muscle has been observed by Jacobsthal in an infant three weeks of age, and calcified lymph nodes in children are by no means unusual. Once deposited it may be again absorbed for Schujeninoff who studied a series of laparotomy wounds in patients who died shortly after operation found that between the ninth and twenty-fourth day seventeen out of twenty-four contained calcified granular deposits. In rabbits similar deposits were formed in the same way, and later largely disappeared. This the writer thought to be a sequel to the colloidal degeneration of the muscle. It may undoubtedly follow many other forms of degeneration, but is especially frequent after hyaline or fatty changes as in the necrotic walls or centers of old abscesses. Considering the notable frequency of hyaline degeneration in tumors of the uterus, calcification is rather rare; and although Klotz and Mönckeberg have upheld the importance of fatty degeneration, it is interesting to observe that calcification in the liver is very rare indeed, while fatty lesions in this organ are a matter of daily observation. Klotz, who has urged the importance of preliminary fat necrosis and the intermediate formation of calcium soaps, also explains the finely granular arrangement of the calcium in the walls of the aorta as a result of the preliminary suspension of fatty globules in the perivascular lymph. He also believes that the frequency of calcification in striated muscle is due to the readiness with which it first undergoes fatty degeneration.

Wells has shown that the chemical composition of normal bone and of pathologic areas of calcification are the same, about

84 per cent. of each being composed of calcium phosphate. This observation gives rise to the question as to whether the preliminary step in the tissue to be calcified is the formation of some substance with a high affinity for calcium, possibly phosphoric acid derived from the degenerating nuclei of the part; and Croftan finds that deutero-albumose, formed during autolysis, has such an affinity.

Another important factor in the chemistry of the situation is the change in local reaction which would permit precipitation of the calcium. For this an increase in alkalinity or at least a diminished amount of carbon dioxide is necessary. Such a change of balance has been used as the chief explanation of the frequency of calcification in the walls of portions of the arterial system as compared to that of the veins where the carbon dioxide content of the blood is higher. This may also account for the phenomenon of "metastatic calcification" or precipitation of calcium from the blood when the content is higher than normal due to bone destruction by tumors, etc.

Wells thinks that a third factor may be the affinity of the under-nourished cells in the semi-devitalized tissue for the serum proteins with which the calcium is combined, thus freeing unusually large quantities of calcium. This author, however, believes, on experimental ground, that the deposition of calcium is dependent not upon the presence of any given chemical substances, but upon specific absorption affinities and physico-chemical relationships only incompletely understood.

Whatever they may be, they are much more regularly encountered than are those necessary to produce the osteoid and osseous tissues. The indispensable factor for this phase is generally recognized as increased vascularity with consequently actively growing fibroblasts in the region of the calcific plaques, this probably being due to irritation, perhaps largely mechanical, but possibly chemical. This is apparently a reparative process which closely approaches, without ever reaching, a neoplastic one, occurring as it does usually in senile tissues in which other proliferative changes are in abeyance and degenerative or atrophic ones predominate. There is general agreement that the process

is one of metaplasia, and that soon after the bony deposits are laid down there are formed foci of cells of varying types, lymphocytes, plasma cells, myelocytes and even erythroblasts are reported, with occasional multinucleated cells of the type normally seen in bone marrow. The source of these cells so rarely seen outside the marrow spaces has aroused much speculation, but Mönckeberg and others are of the opinion that they also are formed by direct metaplasia of the connective tissue elements and are not transported by the blood stream from the normal situations. The absorption of the calcium salts and the deposition of osteoid tissue and eventually fully formed Haversian canals and lacunæ follow just as in periosteal new bone.

In spite of the frequency of calcification in atheromatous blood vessels, ossification is by no means common. It is most often seen in the arteries of the lower extremities in cases of senile or diabetic gangrene, and it is doubtful whether it has ever been observed in a young person, even in those rare cases which have shown calcified and arteriosclerotic vessels. Except in the case of DeWitt in which the femoral vein contained a sheath of bone in the adventitia continuous with an extensive traumatic myositis ossificans, the lesion has not been described in veins. Marchand early mentioned the occurrence of bone in the crural artery and Mönckeberg first described the same lesion in an aorta. Orth stated that the process was less frequent in the aorta than in the other arteries, and its occurrence can in no way be dependent upon the erosion or stimulation of pre-existing cartilage or periosteum or else it might be expected to be more frequent here due to the relation of the aorta to the vertebral column. In the case of Hensen who found bone in the wall of an aneurysmal sac in apposition with the tracheal rings the perichondrium was regarded as the probable source of the bone cells.

The relation of cartilage to the new bone has been studied carefully, but as this tissue is much rarer than bone, except in neoplasms, it has only been found a few times. Rosenstein in 1900 first described both bone and cartilage in a calcified aortic valve, and Marburg in the following year observed minute cartilaginous areas in the intima of the cerebral arteries in three cases,

all of which showed advanced vascular degeneration. Mönckeberg later saw several instances of heterotopic cartilage in the media of the tibial arteries, and Buerger and Oppenheimer mention it as very frequently present. All authors are agreed that it does not necessarily precede the bone formation and has no part in it.

The literature as a whole contains reports of only thirty-five instances of ossification of the arteries: one in the carotid, eight in the aorta, seven in the heart valves, one in the axillary artery, and twenty-one in the extremities. Detailed summaries of these cases are found in the literature, perhaps the most complete being that of Bunting, published in 1906. The case of Poscharissky furnishes the only record of an ossified myocardium. An effort was made by this writer and by Kryloff and Mönckeberg to determine the relative frequency of the lesion by examination of a series of cases. Mönckeberg, who sectioned the arteries in 130 cases, found bone 10 times, or in 7.6 per cent. Poscharissky studied the vessels of 150 persons dying of arterial disease and obtained four positive results, or 2.6 per cent.; while Kryloff found ossification in five of thirty-two calcified arteries, or 15.6 per cent. From these figures it may, therefore, be expected in scarcely more than 6 per cent. of the cases of severe arterial degeneration, and is more than twice as frequent in the lower extremities as in the aorta or heart valves.

PERSONAL CASES

The vessels in the cases presented are sections of the anterior and posterior tibial arteries, one from a case of diabetic, and the other of senile gangrene. The patient in the former case was a man aged sixty-five, who had observed redness and swelling of the left foot for a year, and had suffered considerable pain for the latter six months. The blood sugar ranged from 110 to 152 mg. per 100 c.c. of blood, and the urine usually contained a faint trace of sugar, in spite of a very limited diet. Suppuration of the toes and **tendon** sheaths necessitated amputation in the middle of the calf. A few weeks after this operation it became necessary to remove one toe from the other foot because of the infection which was in progress here also. The middle phalanx of this toe was the seat of an active ossifying periostitis,—a fact which might suggest a tendency on the part of the individual to produce bone in different situations under the influence of certain stimuli.

The arteries of the amputated foot show intimal thickening as well as medial ossification. In most sections the bone extends throughout almost all the circumference and replaces the muscle coat. Its relation to the intima varies. In some sections it seems to bulge forward and encroach upon the



Posterior tibial artery showing ossification of media with endarteritis.

lumen, thus forming the ringed appearance described by Mönckeberg. Elsewhere a few muscle fibers cover the bone and in many of them a heavy layer of fibrous tissue replaces the intima. In other sections a delicate parietal thrombus is attached over about half of the circumference and occupies the greater part of the lumen. This is the usual type of an early organized thrombus containing secondary thin-walled vessels, infiltrating cells and pigment. The structure of the bone is very close to normal although Virchow stated that the cells of heterotopic bone were usually smaller. Osteoclasts are present, though infrequent, and osteoblasts are numerous.

The marrow, which is fairly abundant, is composed of a loose fibrous and fatty reticulum, containing large and very delicate fibroblasts, their nuclei larger than normal, possibly partially due to edema. Polynuclear neutro-

philes, mononuclears, probably plasma cells, phagocytic cells containing hemosiderin and numerous lymphocytes are found throughout. Erythroblasts cannot certainly be identified.

The second case was that of a man aged seventy-four. He suffered for one year from severe pain in both feet. The calves and feet were cold, edematous, and bluish in color, the skin dry, scaling and atrophic. The pulse on the right side was barely perceptible in the popliteal space. After a few weeks, infection and necrosis of the toes of the right foot necessitated amputation of the extremity at the knee.

Both anterior and posterior arteries showed an inflammatory reaction in all of the coats with much disorganization of them; also calcification of the media with ossification, the latter more extensive in the posterior branch. These vessels show some infiltration of the adventitia and a delicate lamina of bone in the outer portion of the media. The inner half is largely calcified, the elastic lamina is swollen, homogeneous and uniformly calcified, and there is an endarteritis which has produced much fibrous tissue and left only a minute lumen patent. The adjacent veins show a chronic endophlebitis. The marrow is well developed around the bone in the larger arteries, much of it being fatty, the rest cellular with myelocytes and normoblasts.

Both of these specimens, therefore, exhibit calcification of the media with the production of considerable quantities of bone accompanied by the usual lesions of arteriosclerosis. Mönckeberg believes that medial calcification is more common than arteriosclerosis, but may occur together with it or as an independent condition and that ossification may be secondary to either. Aschoff thinks it doubtful whether they are truly independent conditions, and points out that no especial etiology is known for either disease, nor can the etiology of the two be separated. Marchand believed that the type of degeneration depended somewhat upon the type of artery, medial calcification occurring in those vessels which were essentially muscular in type with well-developed medial coats; and intimal sclerosis in arteries of the elastic type as the aorta and larger vessels. Kaufmann adheres to this view. The importance of special toxins cannot be overlooked, since it is known that adrenalin may experimentally induce calcification or ossification, or both. But the tendency is strong in many branches of medicine and pathology to explain one uncertainty by means of another equally intangible one, and to assume the presence of an endogenous toxin which, while of great aid in such a discussion, must be under-

stood to possess no basis of demonstrated fact. Whatever undiscovered agency may contribute to the result it is unquestionably augmented by the peculiar exposure of the vessels of the lower extremities to trauma, cold, and the variations in circulatory conditions due to these factors and to gravity.

CONCLUSIONS

1. Ossification of the arteries probably occurs in about six per cent. of the vessels of the extremities which show severe arterial degeneration. It is more than twice as frequent in these vessels as in the aorta and cardiac valves.

2. Ossification of the arteries takes place usually in the medial coat, though occasionally in the intima also.

3. It follows medial calcification with or without endarteritis, but is most common where the two are combined. It is usually not associated with cartilage, but is the result of metaplasia of fibroblasts of the adjacent granulations as they impinge on the calcific plaques.

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Discussion:

DR. MOSCHCOWITZ: Ossification of the arteries has been reported rather frequently. Oppenheimer and Harvey have reported it in recent years. From the analogy to pathological ossification which occurs in other parts of the body, it does not seem to me as if it were necessary to make a separate group for ossification in the arteries. It seems to me that ossification in the arteries follows the general laws for pathological ossification of other parts of the body. The sequence of events is this: death of tissue, which may be either necrosis or hyalinization, calcification, and ossification. Why certain tissues may ossify, while others will not, is a problem that I do not think anybody is able to answer at present. Certainly an exquisite adjustment of the blood supply is one of the necessary factors. More interesting I think than the mere presence or absence of ossification is the genesis. Some years ago I presented a series of five cases of ossification of the ovary. By good fortune these cases presented a continuous series of lesions illustrating the genesis of the ossification very beautifully. I could show that the ossification occurred in the process of angio-genesis—that it was in the process of formation of blood vessels that the ossification occurred; that developing blood vessels presented first on the surface of the ossification in little scalloped portions of the ossification, and that if you followed these developing blood vessels you could see a gradual senescence of the blood vessels, and of the cells which take part in the formation of the blood vessels. These cells are entirely derived from the mesoderm, and are eventually the progenitors of all the cells of the bone, so that not only do these blood vessels form the marrow, but the osteoblasts and bone cells, and the process is very similar to that which is seen in endochondral ossification.

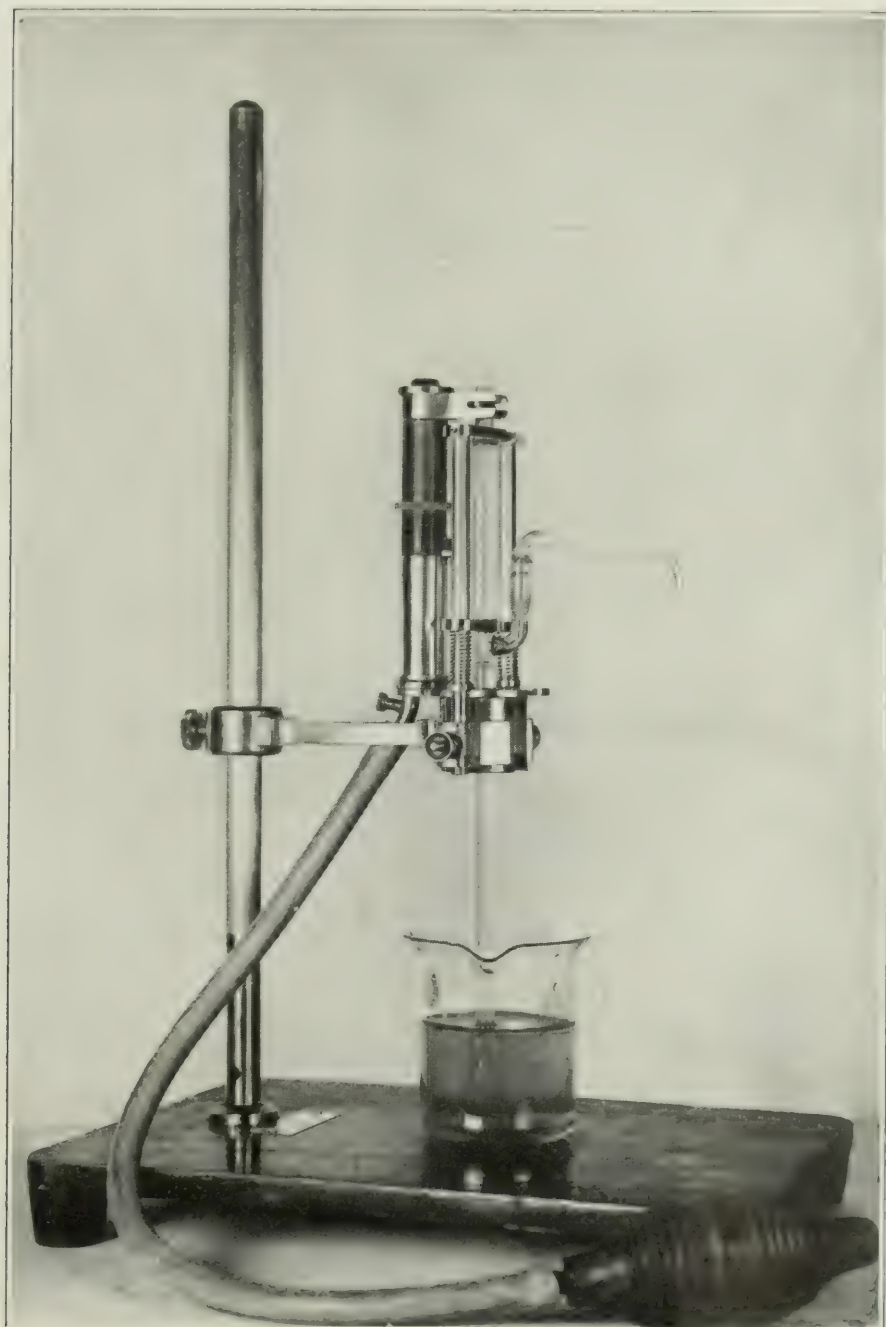
DEMONSTRATION OF AN AUTOMATIC PIPETTING APPARATUS

LEON H. CORNWALL, M.D., AND G. P. SCHMITT

This apparatus was devised to facilitate pipetting. It consists of a glass section through which the liquid is aspirated and delivered and a metal section. The latter functions as the automatic operating portion.

The glass section is composed of a syringe, the distal end of which is continued as a capillary tube. A few centimeters from the distal end of the syringe there is a curved portion of capillary

tubing disposed at right angles to that portion which is a continuation of the syringe. In each arm of the capillary portions there is a bulbous dilatation with a ground joint and a conical



glass bead. These beads act as valves. When one is open the other is closed and *vice versa*.

The metal operating mechanism is essentially a syringe that is operated by forcing air into the barrel. By means of a very simple adjustment the excursion of the metal piston may be regulated for the aspiration of the desired quantity of liquid. The metal piston descends by gravity when the pressure of air is released.

By means of a connecting arm of metal both metal and glass pistons move together. The apparatus may be attached to a ring stand or clamped to the neck of a bottle or flask.

We have used it for Wassermann serology and colloidal gold work at the City Hospital for several months and I can assure you that it saves about 50 per cent. of time in pipetting. Whenever it has been removed it has resulted in vigorous protest from our technical workers. In order to check the syringes we have one graduate for our laboratory standard and we compare each syringe used with this standard. It is presented as a time and labor saving device which substitutes mechanical precision for the inaccuracies inherent in the operation of pipetting by hand.

Discussion:

DR. MACNEAL: Is it possible to adjust the quantities which the syringe delivers?

DR. CORNWALL: Yes, it can be adjusted for any quantity up to the maximum content of the syringe.

PARAGANGLIOMA INTERCAROTICUM

EMIL SCHWARZ, M.D.

This specimen is about one half of the tumor because the surgeon thought it to be enlarged lymph glands. The tumor measured 8x3 cm. The surgeon noticed that there were branches from the carotid artery between the structures of the neck and an attachment of the tumor, so he had quite a difficult time in removing the tumor in his office. The tumor shows a greyish capsule and a whitish parenchyma. It presents the typical structure of a paraganglioma. So far as the surgeon says, the tumor was very well defined, having a smooth capsule. The man was operated on in December, and ever since then has been perfectly well, although the surgeon is sure that he left quite a number of particles of tumor between the structures of the neck.

It is noteworthy that I was not able to demonstrate the presence

of chromaffine tissue in the tumor, although I tried with Grenacher's carmine and with Giemsa's stain, according to the technique indicated in Schmorl. This stain should show a reddish violet protoplasm to chromaffine cells, but I was not able to demonstrate it. I see, however, from the literature that this happens very often.

TERATOMA OF THE TESTIS

EMIL SCHWARZ, M.D.

This tumor is from a man thirty-three years of age, who had noticed a swelling of the testis for about a month. The tumor is very well defined, and showed on gross inspection signs that the tumor was composed of cartilage, bone, and various cystic cavities which might be lined with epithelial structures. Within the substance of the testicle, about 3 mm. distant from the well-defined tumor, one found a small fibrous nodule. The tumor, as it was very well defined, did not indicate malignancy.

Gross inspection indicated a teratoma and the sections confirmed the suspicion. As regards the malignancy of the tumor, I am sure that the proof of the presence of distinct carcinomatous tissue in the above-mentioned nodule, at some distance from the tumor, will leave no doubt that an epithelial portion of the teratoma is spreading as a carcinoma into the surrounding tissue.

I found in the sections a bronchus, also large intestine, goblet cells with high columnar epithelia. As regards small intestine, I am not sure that there were actual villi. There were, furthermore, smooth muscle cells, fibrous tissue, adult and embryonal cartilage, bone tissue, and a stratified layer of columnar epithelium going over into squamous epithelium (probably a "Mundbucht"). In certain portions it looks as if squamous epithelial collections with pearl formation were superimposed on columnar epithelium, so it suggests a metaplasia of a portion of the respiratory tract. At any rate, it is a totipotent teratoma, and does not come within the class of the Wilms tumor as I originally thought it to be when I saw the tumor. It is simply a teratoma with all the structures of the three germinal layers.

Discussion:

DR. WOOD: These teratomata of course are always fascinating to examine and permit a great scope to the imagination in diagnosing the various histological possibilities. Sometimes they form selective metastases. Of course, sufficient time has not elapsed in this case to determine that, but I recall one testicular teratoma in which the abdominal metastases contained striated muscle, an extremely rare occurrence. However, animal experiments often clarify human pathology. In the Crocker Laboratory there is a tumor arising from the sternum of a white rat which contains enormous quantities of striated

muscle fibers, plus some sarcoma. Interestingly enough, the transplants of this tumor after fifteen generations still show striated muscle fibers. This tumor is highly malignant, forming very large masses which often weigh more than the rat which carries it. Such animals seem to be otherwise in perfect health, and there is no clinical evidence of cachexia. I have been watching for about four years a patient with metastases from one of these teratomata, in which the metastasis is apparently largely of the cartilaginous portion. He has a very large and hard abdominal tumor which grows very slowly. He has no cachexia, only some shortness of breath due to pressure on the diaphragm. This enormous mass is a metastasis from a teratoma of the testicle removed five years ago. It resists radiation, showing it is not composed of highly sensitive cells, but is composed of the cartilaginous fraction of the tumor. One of the famous historical cases of so-called pure chondroma of the testicle with metastasis was reinvestigated and found to be a teratoma and not a chondroma, so that instead of it being a metastasizing chondroma, it was really a teratoid tumor.

DR. SCHWARZ: I saw metastasis of a teratoma of the ovary which plainly was of the neuroblastoma type, although at first sight one might have believed it to be a sarcomatous metastasis. Such apparent sarcomatous deposits from a teratoma are probably in many cases derived from neuroepithelium and embryonal nervous structures.

The explanation of such structures as cartilage in metastasis, as Dr. Wood pointed out, is extremely difficult, as such highly differentiated cell complexes are hard to explain when they metastasize. A lot of guessing and diagnosing of normal histological structures has to be done when teratoma or dermoids are examined histologically. It might be mentioned that the persistence of one structure is rather common in the literature, as, for instance, the well-known tooth of Saxer. In such cases, this one element develops often in a malignant way with the suppression of all other tissue elements.

AMEBIASIS IN RELATION TO ARTHRITIS DEFORMANS AND TO HODGKIN'S DISEASE

CHARLES A. KOFOID, PH.D., SC.D., L. M. BOYERS, M.D., AND
OLIVE SWEZY, PH.D.

*(From the Zoological Laboratory, University of California, Berkeley,
California)*

The discussion this evening insofar as it relates to arthritis deformans is based upon the work of Dr. Olive Swezy and Professor Kofoid in stool examinations for the past four years, in the course of which time we have found a number of instances

of coexistences of amebiasis of the bowel and of arthritis, the clinical type of which was, in most cases, unknown to us. Dr. L. W. Ely has recently (1920) distinguished a "second" type of arthritis, which is non-bacterial. Through his kindness we have been able to examine sections of the excised head of the femur preserved in formalin from his case 187. Thin sections of this bone were stained by us in iron hematoxylin and carefully searched. This preparation has revealed not only cells which we interpret (1922*a*) as amebæ, but also has enabled us to find (1922*b*) the supposed ameba in certain phases of mitosis.

The finding of these phases of mitosis enables us to bring forward the most convincing type of morphological proof that these ameboid structures are parasitic amebæ and not merely ameboid human cells. This conclusion rests upon the fact that the type of mitosis in the rhizopods generally and certainly in amebæ of the human digestive tract is a well-marked and peculiar one. It differs in three striking particulars easily recognizable in the proper phases of the process of mitosis from mitosis in the human cells. These phases are brief and prolonged search has been necessary to find them. The fixing of this tissue immediately upon excision has preserved intact in normal cytological condition these evanescent phases of cell multiplication of the ameba.

The three structural features which characterize the phases of mitosis in amebæ are the following. In the first place, the nuclear membrane remains intact throughout the whole process of mitosis. The daughter nuclei arise from the parent one by an equatorial constriction which divides the spherical parent into two spherical daughter nuclei. In the cells of the Metazoa, including those of man, the nuclear membrane disappears at mitosis.

The second characteristic is the presence inside of the nucleus of the centrosome, which in the resting stage lies in the central karyosome of the nucleus. In the prophase of mitosis this moves out against the nuclear membrane and divides into two daughter masses which then migrate to the poles of the nucleus about to divide. During the migration, there forms a deeply staining thread, black in iron hematoxylin stain, which joins the two

daughter polar masses and lies in a meridional position against the inner face of the nuclear membrane. This structure we have called the intradesmose in contradistinction to the paradesmose of flagellate mitosis which joins the daughter centrosomes of the flagellate nucleus. These centrosomes and the paradesmose both lie outside of the nuclear membrane in flagellates. In the case of the metazoan cells, including the human cells, neither intradesmose nor paradesmose is formed. The daughter centrosomes are connected in metazoan cells, if at all, by a cluster of fibrils, lying in the axis of the nuclear spindle and designated as the centrosmose.

The third distinguishing feature is the number of chromosomes which may be counted at the metaphase of mitosis. We have determined the number of these chromosomes in three species of the amebæ of man. In *Endamoeba coli* the number is six (Swezy, 1922). In *Councilmania lafleuri* the number is eight (Kofoid and Swezy, 1921). The number in *E. dysenteriae* (*E. histolytica*, Schaudinn), the etiological factor in amebiasis, is probably six. It does not seem to be in excess of seven or eight, nor less than five. We have not as yet found a sufficient number of favorably placed critical stages to enable us to state the exact number of chromosomes with the certainty with which we have determined it in the other species.

The number of chromosomes which the human cell exhibits in the metaphase of mitosis is, on the other hand, very much greater, appearing to be either twenty-four or forty-eight, possibly both, the former being the diploid and the latter the tetraploid condition. There is little probability of an experienced cytologist mistaking human cells at division with this large number of chromosomes for amebæ having the smaller number. In the light of this cytological and protozoological evidence, we conclude that parasitic amebæ are found in the lesions of Hodgkin's disease. The question at once arises as to whether they are the long-sought etiological factor of this disease or merely a coincident infection without causal relationship.

The cells which we interpret as amebæ in the bone marrow are clustered in the immediate neighborhood of the areas of

pathological activities in the head of the femur, lying just below the eburnated surfaces of the joint, and are not far distant from the hypertrophied bone tissue near the margin of the joint. They are more abundant about capillaries or small blood vessels. They are distinguished not only by pseudopodia, vacuolated protoplasm, and occasionally by evidence of food vacuoles, but also by the fact that the nucleus is relatively smaller than that of most human cells, except those of the eosinophiles, is more uniformly spherical, and has a peripheral film of chromatin attached directly to the nuclear membrane. If this peripheral chromatin is broken up into lobes, these lobes are usually smaller than those found in human cells, such as in the nucleus of the plasma cells. In addition, the nuclei of the amebæ have a solid, spheroidal granule or karyosome, usually central in location, although sometimes ex-centric. The clear zone which lies between this karyosome and the peripheral chromatin is traversed by a few radial, deeply staining spoke-like threads. A narrow clear halo can be detected immediately around the central karyosome in some nuclei, but not in all.

The presence of the amebæ in the territory immediately around the lesions in the bone marrow and closely adjacent to the areas of eburnation and hypertrophy is indicative of the relation between the parasite and the lesions. While the cytological and protozoological evidence here presented is suggestive that the ameba is the etiological factor in Ely's second type of arthritis deformans, investigations along experimental and therapeutic lines are necessary to establish this hypothesis.

The relating of amebiasis to Hodgkin's disease is the result of the joint work of Dr. L. M. Boyers of the University of California Infirmary, Dr. Olive Swezy, and Professor Kofoid. (Kofoid, Swezy and Boyers, 1922*a,b*; Kofoid, Boyers and Swezy, 1922.) At the time of this communication, we have examined the stools thoroughly from seven patients suffering from Hodgkin's disease and have found amebiasis of the bowel in all seven. It is probable that Lincoln's (1908) case of Hodgkin's disease was also attended by amebiasis.

In sections of excised cervical and inguinal lymphatic glands

in cases of Hodgkin's disease, we have found ameboid cells which in nuclear structure, pseudopodia, and vacuolated protoplasm closely resemble cells which we have interpreted as amebæ of the bone marrow. They have similar spherical nuclei with peripheral chromatin, central karyosome, spoke radii and sometimes a halo about the karyosome. Prolonged search of an excised human inguinal gland (Walker's case) removed in what seems to be an early stage of the degenerative phenomena attending Hodgkin's disease, showed a considerable number of amebæ among which we have found certain ones in mitosis. The evidence in this case is similar in nature and extent to that in the bone marrow in the case of arthritis. These ameboid cells have the nuclear membrane intact during mitosis, exhibit an intradesmose, and have approximately six chromosomes.

The human tissue cells dividing in this same gland lose entirely, at mitosis, all traces of nuclear membrane, have no intradesmose, and have a larger number of chromosomes, certainly not less than twenty-four, nor more than forty-eight.

The distribution of the cells which we interpret as amebæ in the excised glands from cases of Hodgkin's disease is suggestive. They are found rather sparingly in and near areas of most active disintegration of the tissues. In some instances the appearance of the nucleus and the cytoplasm of the parasitic ameba is such as to suggest a moribund condition of the parasite. The cytoplasm loses its characteristic vacuolation, the body is rounded up, and the nucleus stains diffusely.

Extensive experimental and therapeutic investigations are necessary in order to establish the hypothesis that Hodgkin's disease is amebiasis of the lymphatic glands.

In the course of over 17,000 examinations of nearly 7,000 persons carried on at the Army Laboratory at New York City and in the Division of Parasitology, Bureau of Communicable Diseases, California State Board of Health, at Berkeley, we have found an unexpectedly high percentage of infection by *E. dysenteriae*, varying from month to month and averaging 16.5 per cent. Some of these persons had travelled in the Tropics, some (2,300) were soldiers who had had some overseas service, some

(576) were home service men (Kofoid, Kornhauser and Plate, 1919), and all of the others were under physicians' care for intestinal troubles, or were being diagnosed for more or less obscure complaints. It is very evident from the nature of our data that amebiasis is endemic in the United States, perhaps somewhat more generally than has hitherto been supposed. These facts as to the distribution and occurrence of this parasitic infection of the bowel of man afford a statistical basis for the occurrence of occasional sequelæ, not only of abscess of the liver, of the lung and of the brain, but, it may be, of amebiasis of the bone marrow and of the lymphatics.

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Discussion:

DR. WOOD: I wish Professor Kofoid had had time to tell many of the other interesting facts which he discussed while we were in my laboratory to-day. I think he has left no step untaken to eliminate any claim not based on pure observation, nor does he make any statement as to the necessary pathogenic relationship of these organisms to arthritis or Hodgkin's disease. Professor Kofoid has placed before us a very important observation, yet I feel that we will have to have very considerable training in order to identify these organisms and to search our material intelligently. Some of these ar-

thritis cases have been well influenced by emetin, which of course suggests that the ameba may have some pathogenic relationships with the disease. That should be investigated, and all of this most arduous work which Professor Kofoed has carried out should be checked thoroughly, and it will be very interesting to see the suggestions he has made followed out, and if the relationship of these two obscure diseases can be settled, I think this is one of the most important presentations we have had before this Society in a long time.

DR. MOSCOWITZ: I happen to be rather familiar with Dr. Ely's material, for he allowed me to study his specimens histologically. There was one thing that impressed me, and that was the remarkable absence of any reactive zone around these areas of necrosis and cyst formation. It seemed to me it was in striking contrast to the remarkable reaction we obtain in Hodgkin's disease, and therefore I think it would be very difficult to explain the pathogenesis of the amebæ in relation to arthritis upon that score alone.

DR. KOFOED: In regard to the point raised, I will call attention to the fact that there was in the bone some distance from these areas a process of exostosis going on, and there was considerable change there. In the study of the lesions in the bowel, one is impressed by the fact that there are territories of considerable reaction of the tissues rather removed from the actual location of the ameba. I was impressed a great deal by the fact that you may hunt through large territories where the characteristic reaction of the tissues has occurred, and find no ameba, but in time you will come to a territory where they are abundant. We need a lot more study on the tissues of the bowel in amebiasis to get the true picture of the process that actually goes on. I think we also need much more help in the process that goes on in the bone. There are a great many puzzling things there, and I wish somebody who is a thoroughly competent student of bone marrow would publish something on the pathology and cytology of bone marrow in all its aspects with especial reference to animal parasites and bacterial infections, and also that we might have something on leucocytes in feces. It would help out the protozoologist very much indeed if somebody would tell us what changes leucocytes go through after they enter the lumen of the bowel. They are one of the pitfalls that beset the protozoologist, for certain eosinophile cells have nuclei strongly like the nuclei of amebæ.

EXTENSIVE DIFFUSE GROWTH OF THE CEREBRO-SPINAL PIA MATER

L. P. RAND, M.D.

(From the Pathological Laboratory, Bellevue Hospital, Dr. Douglas Symmers, Director)

The purpose of this paper is to place on record a case of primary diffuse growth of the pia arachnoid which appears to belong to a rare but well-defined pathological and clinical condition customarily classed as diffuse sarcoma.

The patient, P. McG., aged twenty-two, was admitted to the service of Dr. J. A. Hartwell, of the Second Surgical Division, Bellevue Hospital, on March 23, 1922, complaining of pain in the back, headache, and failing vision. He stated that, while a member of the A. E. F., at Soissons, September 17, 1918, he was thrown in the air by the concussion of a shell, fell on the flat of his back, and was knocked unconscious. On coming to, he found that he could not use his right leg. He was in a hospital for three months, regained the use of his extremity, and ran away to join his outfit. At the end of the war he received an honorable discharge and was well until January, 1921, at which time he developed the symptoms for which he came to the hospital. The pain in his back radiated down the right leg and was often preceded by numbness in the hips and legs. At the Polyclinic Hospital he was given a thorough orthopedic examination, and limitation of flexion of the lower dorsal and lumbar spine was found. X-ray examination showed a faint irregularity between the fourth and fifth lumbar vertebræ, which was diagnosed as an old dislocation. There was also a bilateral papilloedema. He was given a brace which, however, did not relieve him, and he was admitted to Fox Hills Hospital in August, 1921. At that time physical examination revealed nothing new. There were no clear-cut localizing motor, sensory or reflex changes. The cerebrospinal fluid was under decreased pressure, but was otherwise negative, except for a luetic colloidal gold curve on one occasion; the Wassermann reaction was negative. The patient was surly and uncommunicative. Because of the rapidly increasing papilloedema, a subtemporal decompression was performed by Dr. King, which temporarily relieved the vision. No evidence of tumor was found. The papilloedema recurred, and a larger decompression was done, with the removal of a bone flap in the left parietal region. Aphasia and right-sided paralysis developed, but cleared up in two months. Herniation of the brain gradually took place through the bony defect, and from this time on many surgical measures were taken to relieve the increased intracranial pressure, including needle puncture aspirations through the hernia, which gave such relief that the patient continually asked for more. Intensive x-ray treatment was given to check the suspected tumor, and hypertonic salt solutions were given intravenously, as suggested by Cushing, to relieve the intracranial pressure. Ventriculography showed a definite bilateral internal hydrocephalus. Air injected through a lumbar tap was shown by x-ray to pass through the foramen into the subarachnoid spaces under the base of the brain. Another operation was performed, the left ventricle explored, and the region of the aqueduct palpated. No tumor mass was felt, and it was believed that the obstruction was subtentorial. A final operation (April 5, 1922) through an occipital opening revealed a dilated fourth ventricle and a patent aqueduct of Sylvius. The spinal fluid was seen to be clear, while that in the ventricle was deep yellow. However, no obstruction could be found at the foramen of Magendie. Two days later, aspiration through the hernia cerebri to relieve further accumulation gave a cloudy fluid from which a Gram-positive bacillus was obtained. The patient died on April 7, 1922.

Necropsy findings: The postmortem examination was essentially negative, except for the head and spinal cord. The head had been shaved for opera-

tion. In the left parietal region there was a horseshoe-shaped scar, well healed, the convexity upward. Here the skin was rather loose and could be felt to overlie a large bony defect. Over the lower occiput was a T-shaped incision overlying a bony defect removed at a recent operation for suboccipital decompression. An elliptical piece of skin, about 8 cm. across was left adherent to the dura over the parietal bony defect. Aside from this, the calvarium was removed in the usual way. The dura was apparently normal, except where firmly adherent to the skin in the parietal region and where incised at operation in the occipital region. The convolutions of the brain were considerably flattened. There was no increase of fluid over the hemispheres. Extending over a large portion of the basal surface of both hemispheres were partially confluent, grayish-white, rounded, slightly elevated plaques, up to several cm. in diameter, and from 1 to 2 mm. in thickness. The largest accumulation of tissue was over the optic chiasm. The pituitary appeared normal. Over the foramen of Magendie, the arachnoid was slightly thickened, and at one point had been incised at operation. At the site of the parietal defect was an area of cortex, the size of the palm of the hand, which bulged slightly and felt cystic. Here the dura was firmly adherent to the brain. The brain was placed in 10 per cent. formalin, at room temperature, and cut at the end of ten days. The left lateral ventricle was markedly, the right and third moderately, dilated. Beneath a pouched-out area of cortex was a large irregular cavity in the brain substance which communicated with the left lateral ventricle. This cavity and the ventricles were lined by yellowish granulation tissue and contained turbid yellow fluid. The fourth ventricle was perhaps slightly dilated; its ependyma was smooth. The aqueduct was completely plugged by soft grayish tissue. The substance of the brain was riddled with small and large cavities with clean-cut walls, so that the cut section resembled Swiss cheese. The brain tissue adjacent to these cavities appeared altogether normal.

The spinal dura appeared normal. On opening it, the subarachnoid space was found to be distended by pinkish-gray tissue which formed a more or less complete mantle about the cord throughout its length, partially filling the spinal canal. In some portions it was 3 mm. thick. In the cervical and lumbar regions it formed an incomplete covering. Everywhere the development was greatest over the posterior aspect of the cord. There was one discrete, oval plaque, 1x2 cm., on the dorsal surface of the cauda equina. Over this level there was a little clear (?) cerebrospinal fluid. The tumor tissue was soft and homogeneous, and extended along some of the spinal nerves into the foramina.

Microscopical report: Sections through the growth covering the cord and brain show a highly cellular tumor filling the pia-arachnoid space, surrounding the spinal nerve roots and sending prolongations into the processes of the pia in the cerebral convolutions. There is no infiltration of the brain or cord proper. The tumor consists of irregular bundles of varying size, made up of rather closely packed spindle cells. Their nuclei are of medium size, round or oval on section, and stain deeply. In some areas there is considerable variation in size and staining power. No mitotic figures are seen. These bundles

are separated by a loose fibrillar and reticular stroma, taking a pale eosin stain (apparently edematous connective tissue). In many areas the tumor is highly vascular, being rich in capillaries and larger vessels. In some places the tumor cells are thickly placed around the periphery of a medium-sized blood vessel, but this is not a prominent feature of the growth. The bundles of tumor cells lie in intimate relation to the nerve bundles, but there is no apparent connection. Scattered throughout the tumor are areas where the vessels are filled with polynuclear leucocytes, and the surrounding tissue shows a dense or scattered polynuclear infiltration. There are other areas in which are seen groups of large mononuclear cells filled with granular, brownish pigment.

The ependyma of the ventricles is thickened and densely infiltrated with polynuclear leucocytes. Sections of this membrane, stained by the Gram-Weigart method, show Gram-positive bacilli in large numbers, morphologically resembling the Welch bacillus.

Section of the wall of one of the cysts in the white matter of the cerebrum shows closely packed bacilli, similar to those seen in the ependyma, lying in a dense layer close to the cyst border. The nearby vessels contain many polynuclear leucocytes, but there is no other apparent tissue reaction.

Section through the aqueduct of Sylvius shows it to be occluded by recent granulation tissue, densely infiltrated with polynuclear leucocytes and bacilli.

The cysts in the brain substance are apparently "gas cysts" caused by the postmortem invasion of Gram-positive bacilli. It will be recalled that the brain was put intact in formalin, in a warm room, and it is assumed that the cysts were formed before the fixative reached the interior.

I have been able to collect ten cases in the literature of extensive primary diffuse tumor of the meninges (Schultz, Coupland, Hadden, Fox, Virchow, Olivercrona, Nonna, Schroeder, Busch, Markus). If we add to these the cases of sarcomatosis of the meninges where a primary tumor was found elsewhere in the central nervous system with extensive secondary meningeal infiltration, the number is increased to over thirty. As these cases show a similar clinical course and pathological anatomical distribution, they may be included here. The age limits were four to fifty-seven, but the great majority were under thirty. The duration of the disease is usually a matter of months, only two lasting longer than a year. A definite history of trauma was present in several, as in the case here recorded. The clinical course is varied because of the diffuse character of the lesions. In those cases where a large primary tumor was present, local pressure symptoms predominated. Most of the cases simulated a

chronic meningitis, the more acute cases being diagnosed as tuberculous or syphilitic meningitis. Pain in the head and back is an early symptom, often pain and hyperesthesia in the extremities. Later, muscular weakness and paralysis set in. Papilloedema is common, and occasionally there are ocular palsies. In two of Kindsfleisch's three cases there was xanthochromatic cerebrospinal fluid and a high albumen content. This finding has been observed by others.

The autopsy findings in the various cases show a remarkable similarity in the matter of the distribution of the growth. In every case the process consisted of nodular or diffuse infiltration of the pia by a soft, yellowish or grayish pink growth which covered the optic commissure, the inferior surface of the cerebellum, medulla and pons, and passed down the spinal cord, thinly developed, if present at all, in the cervical region, and most marked in the thoracic and lumbar cord. This distribution may possibly be due to the scant room for growth in the region of the cervical enlargement. The growth is almost entirely along the dorsal surface of the cord, though sometimes encircling it. The investing layer is sometimes 1 cm. thick posteriorly. This distribution has but slight variations in all the cases. There is little or no tendency to invade the cord or brain, but the growth may infiltrate the pia mater, even to its final processes. It usually passes out along some of the nerve roots to the foramina. Cerebral involvement causes hydrocephalus in many cases. The only case of true primary meningeal sarcomatosis that metastasized was Olivercrona's case, where nodules were found in the liver and one kidney. The usual method of extension is evidently by the transfer of cell groups, shown by the miliary nodules at the margins of the tumor.

The microscopic findings are rather unsatisfactorily interpreted. The origin of the tumor, if there is a common origin, is obscured by the activity of the growth. Of eighteen cases, six were called small round-cell sarcoma, four spindle-cell sarcoma, one melanosarcoma, two gliosarcoma, two endothelioma, two perithelioma, and one angioblastic sarcoma. There is commonly a multitude of small blood vessels surrounded by tumor cells

in a perithelial arrangement. Ewing believes that this type of growth is best provided for under the designation of diffuse angioblastic meningeal sarcoma. It is believed that probably most of them arise from the endothelial or perithelial cells of blood vessels, or from the endothelium of the pia arachnoid. Certainly the macroscopic picture is a distinct and constant one, and the condition furnishes a clear-cut, well-defined pathological entity.

Discussion:

DR. WOOD: Without microscopical evidence I should be inclined to interpret this lesion as an organization of an extensive hemorrhage following the shell contact in France. It is very interesting. In the gross it would be very difficult to differentiate it from some such lesion. Even the differential microscopic diagnosis between sarcoma and connective tissue hyperplasia is not easy in lesions of this type.

DR. CORNWALL: May I ask if the literature made any mention of antecedent trauma?

DR. RAND: When the cord was taken out at autopsy we did not know whether the lesion was tumor or an excessive inflammatory process, and it was not till the microscopic section was seen that we reached our opinion. However, LeCount, in a personal communication to Dr. Symmers, expressed the belief that these lesions are very possibly inflammatory. I think it was Hadden's case that was reported as a chronic meningitis, but later observers consider his case a sarcoma. The slides of our case need further study, but all of us who have examined them consider the process neoplastic.

I recall two cases in which there was a history of trauma.

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A CASE OF PRIMARY CARCINOMA OF THE URETER

JOSEPH F. MCCARTHY, M.D., AND L. H. MEEKER, M.D.

ABSTRACT

The rarity of primary carcinoma of the ureter prompts the presentation of this case. This brief abstract is to be followed at a later date by a more detailed and comprehensive study of the case.

The patient, R. G., a male forty-nine years of age, was admitted to the New York Post-Graduate Hospital on May 7, 1922. The chief complaint was intermittent pain for four months in the right hip, radiating to the inguinal region. Physical examination was negative except for some resistance in the right hypogastrium. The usual laboratory tests revealed nothing of particular diagnostic significance. The outstanding fact was the obstruction of the right ureter seen by radiographic and cystoscopic examinations.

A tentative diagnosis of ureteral calculus was made and exploratory operation advised. The patient desired the operation postponed, and left the hospital. He re-entered the hospital on June 14, 1922, but was in such poor condition that operative procedure was out of the question. A cord-like mass was palpated, and malignancy of the colon or ureter was suggested. The patient died on July 8, 1922.

Autopsy revealed a tumor mass that encircled the ureter for its entire length, 65 mm. in diameter. Metastatic nodules were found in the liver, lungs, spleen, kidney, pancreas, omentum, heart, skin, etc. Microscopic examination showed the origin of the new growth to be from the epithelium of the ureteral mucosa. Papillary formations filled the lumen of the ureter, and at their base the tumor cells infiltrated all layers of the wall. Metastases were identical with the primary growth.

A diagnosis was made of advanced primary carcinoma of the ureter with extensive metastases.

Discussion:

DR. SYMMERS: Did you find anything in the literature comparable to this?

DR. MEEKER: There are reports of 16 authentic primary papillary carcinomata of the ureter, and I think also 4 of squamous celled carcinomata.

DR. EWING: I have been examining the specimen and puzzling over the diagnosis. It seems to me that on account of the size of the tumor and its relations conclusions are rather difficult to draw. Of course the clinical history is rather unfavorable to the diagnosis of primary carcinoma of the ureter. I would like to hear the opinion of the surgeon. The tumor undoubtedly shows transitional epithelium, of which there are many areas. The absence of a definite source in any other organ and the extensive involvement of the ureter would seem to lead by exclusion to the idea that it must arise

in the ureter. One of the most remarkable features of the case is the very active growth and the hemorrhagic character of the "red" portions, so-called, and also the reproduction of this hemorrhagic character due to the many dilated blood vessels in the numerous metastases. The body was literally riddled with metastases. I think Dr. Meeker's conclusion is correct. She has a very remarkable case of extremely extensive generalized primary carcinoma of the ureter.

DR. MCCARTHY: I recently presented six cases of papillary new growths of the renal pelvis, one of which involved the ureter, and in all of which there was hematuria. It seems to me that the papillary nature of the growth might lead to the conclusion that it did take its origin in the ureter. We urologists are apt to be a little conceited about our certainty in diagnosis until we encounter a case of this type. When this case first came under observation there was more or less well-defined tenderness in the region of the appendix; we thought of the possibility of a new growth of the colon, but as you noticed in the x-ray reports, there was so much distension with gas that no one of the pictures was satisfactory. Another interesting thing was the absence of pus in the urine. One would rather expect pus and blood in the urine in a case of this type, and it is this type of case which offers great difficulties in the way of diagnosis, short of exploratory operation. Where we can make a ureteropyelogram the diagnosis is relatively simple. In my opinion the case is definitely one of primary new growth of the ureter. I had never encountered a case like it before, nor heard of one for that matter, until Dr. Robin, one of our best investigators at the Academy, brought us case reports from everywhere. I think there were twenty-odd cases, some of which were not primary, but probably fourteen or fifteen of them were definitely primary new growths of the ureter, not taking their origin in the renal pelvis, but definitely in the ureter.

DR. MEEKER: I would like to call attention to the fact that no tumor previously reported is anywhere near as bulky as the one presented here.

XANTHOMA (XANTHELASMA) OF THE TONGUE

ELI MOSCHCOWITZ, M.D.

The patient, aged thirty, presented himself to Dr. Walter M. Brickner because of a tumor of the tongue which he had noted for some months. It was on the dorsal surface, round, hard, slightly elevated, yellowish, and about 1 cm. in diameter. The tumor was removed without trouble.

Microscopically the tumor presented a most unusual appearance which was frankly puzzling. I am indebted to Dr. F. C. Wood, who finally established the diagnosis of xanthoma. The growth lies at some distance beneath the epithelial layer from which it is separated by normal muscle fibers. There is no capsule, the xanthomatous tissue spreading irregularly into the surrounding muscle structure. The tissue consists of extremely large pale cells with a finely granular protoplasm staining faintly blue with hematoxylin. They

are irregularly round or oval, the cell outlines are faint and tend frequently to merge together so that great irregular granular syncytial plaques are common. The whole structure makes one understand the designation "foamy tumors" that has been applied to this tissue. Sharply staining, large, oval or quadrilateral nuclei are abundant, but their relation to individual cells is often indeterminate. In general they appear most abundant on or just beneath the cell membrane. Of significant interest is the fact that the structure is not homogeneous. Scattered throughout the tumor are numbers of muscle fibers, in bundles and individually. Close study with the higher powers shows distinct xanthomatous degeneration of the muscle fibers. An intact muscle fiber can be seen gradually to lose its striated appearance; the distinct eosin pink of the fiber gradually merges into the faintly blue xanthomatous tissue. At the same time the fiber swells appreciably and the delicate sarcolemma becomes the outline of the xanthomatous cell. The muscle nuclei become slightly smaller, but do not otherwise partake greatly in the change. Not infrequently one recognizes a large longitudinally placed xanthoma cell containing a small segment of well-stained muscle fiber showing the gradually xanthomatous degeneration on either end. In a sharply defined muscle bundle, one portion shows xanthomatous degeneration; the remainder is intact.

According to all morphological criteria, therefore, this "tumor" represents a xanthomatous degeneration of muscle fibers. The term "xanthoma" is divided by dermatologists into two varieties, xanthoma planum or palpebrarum, and xanthoma multiplex. Inasmuch as the latter presents itself as hard nodules the term "tuberosum" has been added. Xanthoma palpebrarum is familiar in elderly people on the eyelids, especially near the inner canthus, forming the so-called chamois-like deposits. Xanthoma multiplex or tuberosum is rare, and is present on various portions of the body, especially around the exterior surfaces of the elbows and knees, the palms, the trunk, and even the eyelids. Lesions have been described in the internal organs, the mucous and serous membranes, tendons, trachea, esophagus, liver, heart, aorta and spleen. It frequently begins early in life and is sometimes congenital and, according to Fletcher, four-fifths of the cases are accompanied by chronic jaundice. Diabetes is also not an uncommon accompaniment. The so-called xanthoma diabeticorum is not a separate variety of the disease.

For many years the lesions of both xanthoma palpebrarum and multiplex were considered identical. Both were supposed to be the result of a fatty or lipoid degeneration of connective

tissue structures. We are indebted to Pollitzer, who has made some of the most important contributions to the study of xan-



FIG. 1. Low power.

thoma, for a sharp differentiation between the two lesions. Pollitzer showed that xanthoma multiplex is the result of a xan-

thomatous infiltration of the adventitial connective tissue cells of the papillary and subpapillary layers of the skin which take up

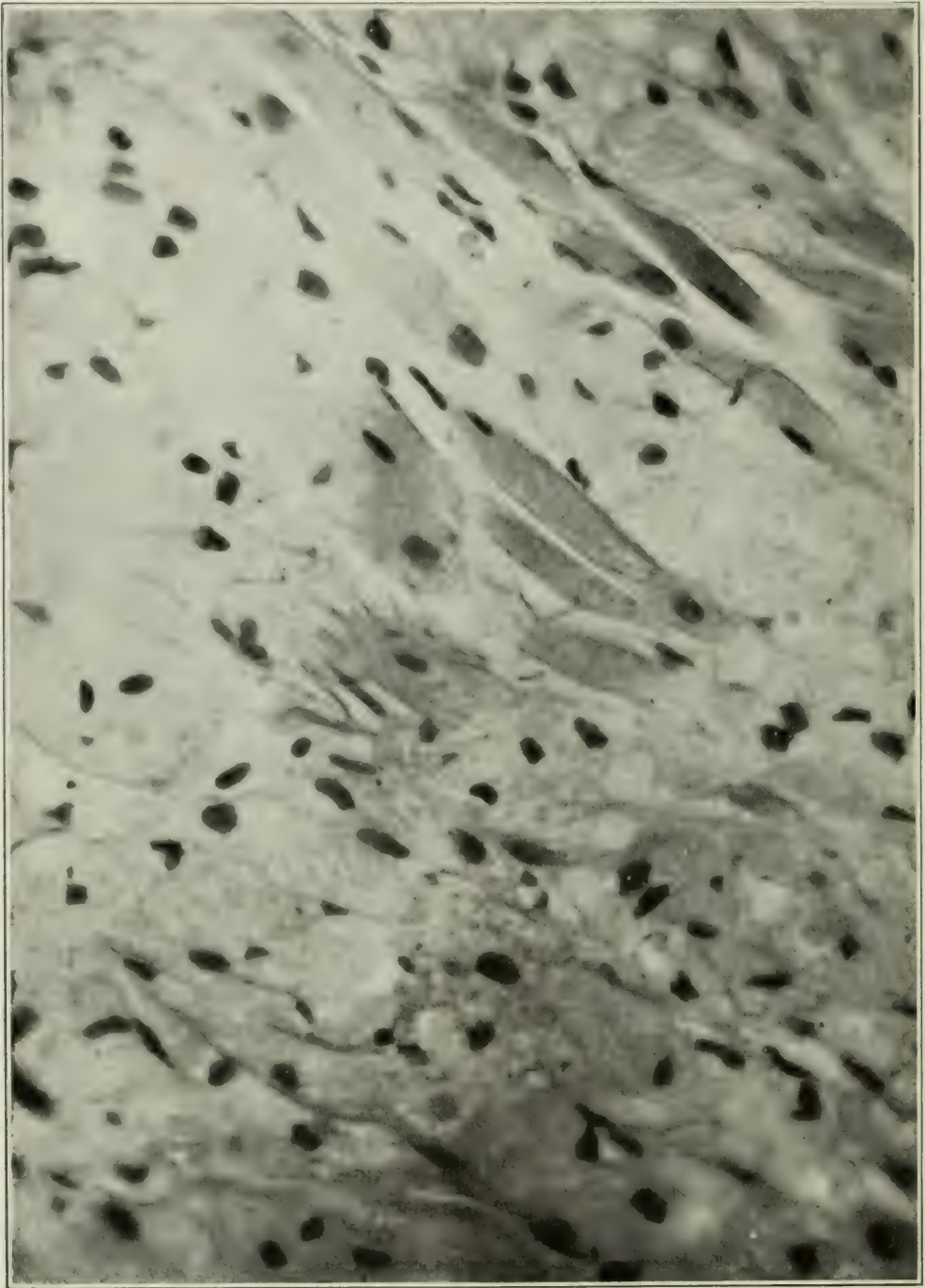


FIG. 2. High power.

lipoid substances from the blood vessels. In xanthoma palpebrarum, on the other hand, the lesion consists in a xanthomatous de-

generation of the fibers of the orbicularis muscle. The specimen which I present seems therefore to be most unusual and histologically must be classified as a "xanthoma planum."

The manner whereby xanthomatous tumors are formed is a much debated and perplexing subject. It seems to be well agreed that the xanthomatous material exists in the form of a cholestero-fatty acid-ester. Pollitzer makes the explanation that this substance is present in the blood in excess in cases of jaundice and diabetes and is deposited in cells in those situations where friction and trauma are most likely to occur. However, Rosenbloom and Rosenthal and Braunisch in a very recent study failed to find a cholesterinemia in xanthoma multiplex.

Xanthoma of the tongue is rare. Butlin, in his work on "Diseases of the Tongue," describes a patient who was jaundiced and presented numerous xanthomata. On the side of the tongue were two yellowish oblong patches, raised, soft and varying in size from a pea to a sixpence. Smith in 1912 reported another case similar in structure to the one here reported. These are the only cases I have been able to find.

Discussion:

DR. POLLITZER: Xanthoma has attracted very little attention on the part of general pathologists; the condition is rare, and in general of very little importance. Perhaps it is for this reason that the confusion between what is called xanthoma tuberosum and xanthoma planum that arose from the unfortunate association of the two forms in one of the first cases described by Addison in 1850 has gone on down to the present time. Practically all the books on dermatology and pathology adhere to a subdivision into two forms, the tuberoso, or generalized, and the plane, or palpebral form. And yet the clinical differences between these two conditions are so striking that on clinical grounds alone it seems to me obvious that the two processes have nothing in common except a yellow color. Xanthoma occurs as prominent, hard, round, or lobulated tumors; xanthelasma (a name I have suggested should be used distinctively for the plane form) is a flat, soft discoloration, indistinguishable on palpation. Xanthoma occurs at any period of life, but usually in early adult life and childhood. It develops rapidly, in a few weeks or months, disappears after months or years, or undergoes fibrous changes and persists indefinitely. Xanthelasma is practically unknown before middle age; its development is slow, extending over years; once established, it persists throughout life; it never undergoes fibrosis. Xanthoma is extremely rare; xanthelasma quite common. The lesions of xanthoma occur anywhere on the general integument with the

neighborhood of the large articulations as the seat of predilection. (Under the tense epidermis of the palms the tumors may be spread out in striae along the normal folds.) Xanthelasma is limited to the face and neck, the region of voluntary cutaneous muscles, and in rare instances has occurred on the tongue, the uvula, etc.

Histologically, xanthoma is an irritative connective tissue cell hyperplasia due to the presence of cholesterol fatty-acid esters derived from the blood. The process begins with the extrusion of cholesterol into the vascular adventitia whose cells take up the lipid particles, increase in size and proliferate, sometimes becoming multinucleated. The cells, arranged in masses around a blood vessel, act as stimulants to the production of fibroblasts, resulting in old xanthomas in the development of fibromas which have been erroneously interpreted as the primary tumor, xantho-fibroma. Xanthoma connotes a systemic disease, a disorder of metabolism of which cholesterolemia is the most obvious symptom. The fact that different observers have reported discordant results in their estimation of cholesterol in the blood in these cases may readily be accounted for on the ground that the cholesterol may be present in excess only during the stage of active formation of the little tumors, which will persist, however, after the cholesteremia which occasioned their development has disappeared. It is nevertheless a fact that extremely high figures for cholesterol in the blood have frequently been recorded in these cases, 6 grams or more per thousand.

In xanthelasma on the other hand there is no evidence of a metabolic disturbance. The highest figures recorded in simple cases of xanthelasma are just about on the upper level of the normal for cholesterol, 1.90 per thousand. Histologically there is no sign of connective tissue or other inflammatory change. In studying the histology of xanthelasma I earnestly advise that the anatomy of the normal eyelid be studied first. In the normal eyelid there is an extensive layer of striated muscle fibers filling the space between the epidermis and the subcutis. In old cases of xanthelasma this layer of muscle fibers has almost completely disappeared and in its place we find the so-called xanthoma-cells and masses. It is only in recent cases of xanthelasma that the relation of muscle fibers and "xanthoma" cells can be clearly made out. In early cases we find abundant muscles showing degenerative changes; the fiber loses its striations, becomes glassy in appearance, sarcolemma nuclei proliferate, the muscle substance becomes clumped, and takes stains irregularly; finally fatty particles are disclosed and the muscle breaks up, the sarcolemma sheath however persisting. These changes frequently may be followed in a single fiber cut longitudinally and most of them are beautifully shown in the sections of xanthelasma of the tongue before you under the microscope. The few cases of this peculiar degeneration occurring on the tongue, the uvula and in one case in a congenital pendulous myoma have been regarded as xantho-myoma. The term implies a tumor of the muscle fibers, but as a matter of fact, there is no increase of muscle fibers in these cases, but on the contrary, as is obvious in the eyelid lesions, a disappearance of muscle fibers.

In conclusion, I should like to say that there is no ground for the current

subdivision of xanthoma into two forms, planum and tuberosum. These two conditions are totally distinct processes, the one a connective tissue pseudo-tumor, the other a focal degeneration of striped muscle fibers. For the one the name xanthoma may be retained; for the sake of clarity the other should be given a different name. I have proposed that the name xanthelasma be retained for the myogenetic form. The case shown by Dr. Moschcowitz is not a xanthoma, but a xanthelasma of the tongue.

DR. ROHDENBURG: In a case of hemachromatosis in a female, who quite incidentally developed a series of xanthomata on the eyelid and in various portions of the face, the diagnosis being confirmed by removal of some of the specimen, during the acute stage this woman had a blood cholesterol of 800 mg. per 100 c.c. of blood. About three weeks after the acute stage had subsided she had a blood cholesterol of 250 mg.

DR. SYMMERS: Incidentally hemachromatosis in a female is an extremely rare phenomenon.

CARCINOMA WITH GRAVE ANEMIA

A. V. ST. GEORGE, M.D.

(From the Pathological Laboratory, Bellevue Hospital, Dr. Douglas Symmers, Director)

The following case presents a rather interesting and by no means undisputed clinical condition.

The patient, a white male, fifty-seven years of age, nationality Swedish, occupation stableman, was admitted to Bellevue Hospital in May, 1920, when a diagnosis of pernicious anemia was made. At that time he had lost weight and presented the typical blood picture of pernicious anemia. He was re-admitted on March 12, 1921, and stayed in the hospital until March 31st, when he was again discharged, at his own request, condition unimproved. On May 24, 1921, he was again admitted to the hospital with the following history:

Since the previous admission, he had not felt well at any time, and recently had developed pain in both legs and in the right chest; he did not work for five weeks. Weakness, emaciation and dyspnoea were the chief symptoms.

Physical examination showed a thin, emaciated male, of pale yellow complexion, who looked chronically ill. The mucous membranes were very pale; eyes, nose, mouth, neck and lungs were negative. The heart showed a diffuse apex beat in the fifth interspace, 9.5 cm. from the mid-sternal line. The heart was not enlarged. Diastolic blowing replaced the first sound and followed it at the apex. There was a systolic blow at the pulmonic area. The heart was regular in rate and rhythm. The abdomen was negative. The arteries were thick and beaded. Examination of the eye grounds showed the discs pale; there were old and new hemorrhages in both eyes.

During the patient's stay in the hospital he became progressively weaker and, during the last days of life, he was partially irrational. The pulse ranged

from 114 to 130; temperature from 97 to 98.4. The urine was negative; the Wassermann reaction was negative. The red count was persistently low, with a low leucocyte count. On the last day of life the count was as follows:

Hemoglobin.....	10 per cent. (Dare)
Red cells.....	460,000
White cells.....	2,000
Polymorphonuclears	40 per cent.
Lymphocytes.....	51 per cent.
Many normoblasts and poikilocytosis.	
Polychromatophilia.	
No megaloblasts seen.	

Gastric analysis showed no free hydrochloric acid. The clinical diagnosis was pernicious anemia.

Autopsy No. 7343: The body was that of an emaciated white male of good development, five feet, nine inches in length, weighing about 110 pounds. The subcutaneous fat was very scanty and lemon-yellow in color. The heart was large and flabby and contained thin fluid blood. There were no changes in the valves. The myocardium was yellowish and friable. A network of yellowish striations was visible under the endocardium—the so-called tiger striping. All the chambers of the heart were dilated. The kidneys were slightly enlarged and, on cutting through the capsule, the kidney substance bulged. The pelves were filled with a large amount of lemon-yellow fat, and the markings were largely obscured. The liver was normal in size, somewhat reduced in consistence, and had a yellowish color. There were no signs of siderosis. On the mucosa of the greater curvature of the stomach, two inches from the pylorus, was a soft, irregular mass, about one inch in diameter and extending into the stomach for three-quarters of an inch. The surface of the most prominent portion was covered with dark red blood and appeared ulcerated. For a distance of one or two cm. around the mass, the mucosa appeared thickened; elsewhere it was normal. The bodies of the vertebræ contained considerable red marrow. The long bones could not be opened in this case.

Anatomical Diagnosis: Dilatation of heart; fatty degeneration of myocardium (tabby-cat heart); hydrothorax (bilateral); partial atelectasis of lungs; old tuberculous nodule of right lower lobe; edema of visceral pleura; chronic parenchymatous nephritis; fatty degeneration of liver; adenocarcinoma of stomach; atheroma of aorta; red bone marrow; anemia of pernicious type.

Histology: Microscopic examination of the growth from the stomach showed a typical well-formed adenocarcinoma with ulceration.

Pernicious anemia as a distinct clinical conception in association with carcinoma of the gastro-intestinal tract has been reported both in the foreign as well as in our own literature. In the reported cases, a small ulcerating carcinoma of the stomach was generally an accidental finding at autopsy. But whether the

carcinoma is the primary disease and produces the picture of pernicious anemia, or, secondly, whether it is merely incidental and coexistent, or, thirdly, whether we assume that the achylia gastrica of pernicious anemia prepares, so to speak, the gastric mucosa for the development of a carcinoma, is a problem still unsolved. Can a carcinoma produce an anemia of such magnitude as to give a blood picture of pernicious anemia? The answer must be yes. Cabot, in discussing this question, presented a series of gastro-intestinal cancer cases in which there was no anemia whatever. He states that whenever the anemia in carcinoma attains a picture simulating the pernicious type, we generally find leucocytosis and relatively few, if any, megaloblasts. It will be noted that in our case no leucocytosis was encountered. In the differential diagnosis of the two conditions, Cabot urgently advises not to make the diagnosis from the blood picture alone.

Recently Hartman reported a case in which blood changes simulating pernicious anemia developed in a gastrectomized patient (gastrectomy for carcinoma). He also refers to one other case reported by Moynihan. He suggests, in view of this experience, that the absence of the gastric enzymes may play a rôle in the production of pernicious anemia.

In an interesting study of the anemias accompanying carcinoma, Roessingh found that new growths arising from skin or mucous membrane invariably showed an anemia. New growths in other structures followed no such rule. He quotes Verse, who in an accidental finding of twelve tumors of the gastro-intestinal tract, none of which measured larger than 11 mm. in diameter, stated that four showed macroscopic and the remainder microscopic ulceration. Statistics indicate that at least 92 per cent. of intestinal new growths give a positive chemical reaction for blood in the stools. The presence of blood in the feces in a case of suspected pernicious anemia is, therefore, of importance. Roessingh further attaches great weight to the determination of the bilirubin content of the blood in carcinoma and states definitely that, except in cases where there is a primary or metastatic new growth in the liver causing obstruction to the

bile flow, there is never an increase in the bilirubin content of the blood, and hence there can be no real blood destruction. Unfortunately, this was not determined in our case, though experiments now in progress with the test tend to confirm Roesingh's results.

It is interesting to note that in all reports of pernicious anemia with an accompanying tumor, the tumor was located in the gastro-intestinal tract.

In conclusion, it cannot be definitely stated whether carcinomata of the gastro-intestinal tract produce a blood picture simulating pernicious anemia. From the fact that practically all gastric carcinoma patients present a constant melena and that repeated small bleeding of experimental animals produces an aplasia of the bone-marrow, it is conceivable that this factor alone, and quite independent of carcinoma toxins or gastric atrophy, exhausts the bone-marrow to such an extent as to produce a pernicious anemia picture. How long the patient in our case had the tumor is also not determinable.

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Discussion:

DR. STILLMAN: I think the point Dr. St. George has emphasized is important, that a definite diagnosis of pernicious anemia may be extraordinarily difficult. The blood picture in these primary carcinomata of the gastro-intestinal tract is at times identical with that found in pernicious anemia. I do not know whether I quite understood Dr. St. George to suggest that the anemia might be due to hemorrhage from the tumor. It seems to me that it is difficult to accept that. The work that has been done recently at the Rockefeller Institute in regard to the changes which take place in the bone marrow following repeated hemorrhages shows that it requires more than simple loss of blood to produce the activity of the bone marrow we find in pernicious anemia, and that we find also in these cases of tumor. It is more than loss of hemoglobin. Apparently there is a toxic factor in addition. I think Dr. St. George is quite right in saying that the diagnosis of pernicious anemia here is an exceedingly questionable one, and it is much more probable that the anemia is associated with the tumor growth.

DR. FRIEDMAN: I believe that if repeated bleeding alone could be the cause of pernicious anemia, you would see in carcinoma the picture of pernicious anemia more frequently. I remember one case in my student days which was diagnosed by Dr. Staddman as pernicious anemia, and at the autopsy by Professor Thoma a carcinoma in the posterior wall of the stomach was found. I do not know what the examination of the bone marrow showed, but pernicious anemia is very frequently confused with carcinoma. As to achylia gastrica, I do not believe that it predisposes to carcinoma. I have seen a number of achylia gastrica cases. Some of the patients I have examined ten or twelve years later, and I have always found the same condition of achylia gastrica. I do not remember in all of my cases that any one of them developed carcinoma or pernicious anemia while they had achylia gastrica.

DR. MOSCHCOWITZ: It seems to me that the question is entirely academic as to whether the patient had primary pernicious anemia, or whether he had carcinoma with the clinical picture of pernicious anemia. There is no doubt but that the blood picture characteristic of pernicious anemia can be caused by definite known things, *e.g.*, the *Bothriocephalus latus* infection. There is also no doubt but that carcinoma of the stomach can give the identical picture. The only reason why we make a differentiation is because we know the cause of one, and we do not know the cause of the other. Primary pernicious anemia is only called "primary" because we do not know the cause. I think the wisest point of view is to regard pernicious anemia as a syndrome which may be due to a definite and to an unknown cause.

DR. DENTON: In regard to the bleeding in pernicious anemia, Dr. René Mouchet and myself reported a case of two negroes in the Belgian Congo, who were really property of the Government. We wanted to decide whether they had sleeping sickness or not. We drew twelve c.c. of blood from each of these two patients every day for thirty-four days. At the end of this period we became alarmed at the appearance of the two negroes and examined their blood. One of them, an apparently normal negro with the exception of the suspicion of sleeping sickness which was not in any sense certain, developed a typical picture of pernicious anemia with both large and small nucleated red cells. The quantity of blood taken out of the man was not large as compared with what is drawn in transfusions, when they take from 1,300 to 1,500 c.c. of blood at one time. The other negro did not show the nucleated red cells, but he did show a rather marked anemia for the amount of blood which had been taken out. I admit that this is not definite, because of the countless negroes that we autopsied over there nearly all showed hookworm. That is one possibility that we could not exclude, but there was a great difference in the appearance of the two men after taking twelve c.c. of blood from each of them for thirty-four days.

DR. SYMMERS: What happened when you ceased taking the blood?

DR. DENTON: They became all right again.

DR. EWING: This discussion brings up the question, what is the essential element in pernicious anemia? I am rather interested to hear in the New York Pathological Society, which is devoted to the study of pathological

anatomy, a discussion which fails to consider the essential lesion of pernicious anemia in the bone marrow, and I think that the whole discussion would be cleared up if one recognized, what I believe to be the truth, that pernicious anemia consists of an abnormal formation of blood in the bone marrow, and that when we can demonstrate histologically this abnormal formation of blood in the bone marrow we have established the diagnosis of pernicious anemia. Therefore I think that we must have a report of the bone marrow in this case. There may be quite a variable picture in the bone marrow of pernicious anemia, and we have not this evidence in the case presented. It is clear that pernicious anemia sometimes follows hemorrhages. Progressive fatal anemia is not so very infrequent with bleeding carcinoma in various parts of the body.

DR. ST. GEORGE: It is a well-established fact that investigators, after taking about five c.c. of blood from animals for about two weeks, have produced the blood picture of an anemia of the pernicious type. I think the same picture is probably to be seen in any case of carcinoma, provided the disease has lasted sufficiently long. Whether it is produced by a toxin derived from the growth, I do not think anybody can answer. In this case none of the clinicians who saw the patient thought of a carcinoma. If this small growth had been taken out, the patient's life might possibly have been saved, provided he did not have a true primary pernicious anemia.

CARCINOMA OF THE APPENDIX: FIBROSARCOMA OF BACK: ADENOCARCINOMA IN CURET- TINGS OF UTERUS

D. S. D. JESSUP, M.D.

The specimens for demonstration were thought to have features of sufficient interest to warrant their presentation to the Society.

The first specimen is an appendix removed in the course of a routine operation in a case of cholecystectomy. The patient was a physician, sixty years old, who had always been in good health and had had no surgical or medical diseases except an attack of gall stones some thirty years before. The appendix on examination appeared like a normal appendix, and it was only on microscopical examination that we came across a rather unusual picture. Microscopically the mucosa is entirely replaced by a growth of large, irregular glands, with entire loss of the normal structure of the mucosa and the lymphoid tissue, so that everything is destroyed out to the muscularis. This is not invaded. The cells are filled with mucus, and with different stains give different appearances. With a deep hematoxylin stain they look very dark in color, and with a light stain they give more of the idea of cells filled with clear mucus. The lumen of the appendix is filled with broken-off glands. Only at the proximal end is there any normal structure of the glands.

The question comes up as to whether this is a true tumor, and should be placed under the classification of adenocarcinoma, or whether it should be called a mucous degeneration or proliferation, and should be likened to a polyp in other portions of the intestinal tract. We see this same proliferation of mucus in carcinoma of the rectum and other portions of the large intestine, where the cell structure is almost entirely lost, and we have nothing but large quantities of mucus with only occasional gland structures persisting.

The second case is one of what under ordinary conditions would be looked upon as a rather common tumor—a fibrosarcoma, and the interesting point here is as to whether it presents the histological evidence of malignancy. It is a type of tumor one sees often in the skin and subcutaneous tissues of various portions of the body, and we are often puzzled as to whether it should be called a fibroma, or fibrosarcoma, or a spindle cell sarcoma. I have no lantern slides of this case, but it has the ordinary appearance of a cellular fibroblastic tumor, the cells arranged in bundles, interlacing, and uniform in size. It is a well-encapsulated tumor; there is some ulceration on the surface.

As to the clinical history of the case, the patient was a woman of twenty-five, who at the age of nine years noticed a small lump on the back. This increased somewhat for a number of years until 1917 it reached the size of a walnut. The skin over it was normal. Five years ago she had an operation at Mount Sinai Hospital for the removal of the tumor. It recurred three years later, was then the size of a cherry, situated to the left of the original incision. She was treated for a period of three years with radium at the Radium Institute, for one year by radium alone with the removal of the tumor, and then treatment again with radium. During the last year the tumor was removed twice. At the Skin and Cancer Hospital we did the fifth removal with recurrence. This illustrates the recurrence of those tumors which have histologically the appearance of benign tumors.

The third slide which I have to show is one from a case of curettings in which from the histological appearance we made a diagnosis of adenocarcinoma or malignant adenoma of the uterus. The woman was fifty, with a history of some irregular bleeding between the menstrual periods, and with a small polyp at the cervix. The operation was for removal of the polyp. The hemorrhage was thought to be due to the presence of the polyp. It was small, and was not kept separate from the other curettings during the operation. In this case the picture seems to me sufficiently different from the normal

endometrium in any of the various stages of the menstrual cycle to justify a diagnosis of a malignant condition.

Discussion:

DR. WOOD: I think the appendix is a very interesting specimen, but we never shall know whether it is a carcinoma unless the patient develops a recurrence. It is a type of neoplasm rarely seen in the appendix. The mucocoeles are often extremely difficult to diagnose, because they dissociate the muscle fibers and the cells grow out between the fibers of the coats, giving the appearance of true invasion, such as we see in malignant tumors of the gut. That has not occurred in the growth under discussion. But I have seen specimens of the mucocoele type in which it is perfectly impossible to say if it was a gelatinous carcinoma of the type frequent in other portions of the gastro-intestinal tract. I am inclined to think from the invasion of the muscularis, and from the general morphology of the cells seen in carcinoma of the rectum, that we are dealing with a true beginning carcinoma of the appendix. It is obviously entirely different from the well-known carcinoid growths, about which there is so much discussion.

The sarcoma illustrates a very important point. We pathologists are constantly being handed specimens by a surgeon and asked to make a prognosis. It is a very dangerous procedure to make a prognosis. It is certainly possible to do so for instance in a neurofibroma which is almost always called malignant by the average pathologist who has not had much experience. I often see such specimens where a diagnosis of sarcoma has been made on cellular neurofibromatous nodules which have been widely removed. This tumor at its present stage of course is a sarcoma. You see occasional mitotic figures, and the irregularity of the nuclei which suggest the diagnosis of sarcoma. I have seen such specimens where at the initial incision no such diagnosis could be made. The nuclei were all regular in distribution, size, and shape, the amount of interstitial tissue very large; there were no mitoses, and not the slightest evidence of anything malignant. After one recurrence they become more cellular, and after four or five they become still more cellular. I have seen the so-called myxomata go through years of recurrence, each return getting more and more cellular, until the final stage was a general invasion of the body with a highly metastasizing tumor. Of course this tumor should have been widely excised at the initial operation on the patient, and it thoroughly illustrates the point that there is only one time to do surgery, and that is the first time. There is still too much poor surgery being done at the best hospitals and by the best men in the City of New York. They do not realize that there is only one chance in cancer surgery. I think using radium and x -ray on these tumors, while interesting as a matter of research, does not cure them. They are highly resistant to these agents. A guinea-pig fibro-sarcoma now growing at the Crocker Laboratory will resist nine or ten erythema doses, which means if the patient had that tumor the necessary dose of x -ray would kill the patient. Even by burying radium needles, sloughs may be produced in these tumors, and a portion of them destroyed, but we cannot affect the whole tumor by radiation, in which case radiation is no better than cutting the tumor out.

The last specimen of Dr. Jessup's, it seems to me, is a very early adenocarcinoma of the uterus, and an interesting specimen from that point of view.

A CASE OF PRIMARY TRICUSPID ENDOCARDITIS

CLARENCE DE LA CHAPELLE, M.D.

Among 8,373 autopsies at Bellevue Hospital, this is the fifth case of endocarditis confined to the tricuspid valve, and hence seems sufficiently rare to be worth reporting. The four previous cases were reported by Dr. St. George, together with a fifth case which he had encountered in a series of 429 autopsies in the American Army.

The patient, a man, aged fifty-five, was admitted to Bellevue Hospital on May 17, 1922, complaining of pain in the right chest, cough, and expectoration of bloody sputum. He gave a history of having been drinking heavily for several weeks and of having been exposed to dampness while at work. There was no history of rheumatic fever or tonsillitis. He had had malaria twenty-five years ago.

On admission the temperature was 101.8° F., pulse 104, respirations 24. There was dulness in the right base and broncho-vesicular breathing with crepitant râles and increased voice sounds in the right axilla. The diagnosis of lobar pneumonia was made. The left border of the heart percussed 11 cm. from the mid-sternal line in the fifth intercostal space. No definite murmurs were heard but the heart sounds were distant; rate 78, rhythm regular.

On May 27 the patient had a chill lasting thirty minutes; the temperature was 98.8° F. at this time. Four days later dulness was elicited over the right upper and middle lobe with bronchial breathing and bronchophony. Diagnosis: Unresolved pneumonia.

On June 15 the patient had another severe chill of malarial type according to the note on the chart. No malarial parasites were found in the blood smears. The blood pressure was 102 systolic; 68 diastolic. The urine showed a trace of albumen and a few white blood cells. An x-ray, taken about this time, showed marked fibrosis of the right upper lobe with retraction of the trachea to the right, but no other evidence of infiltration or consolidation was seen.

A week later the heart sounds were clearly audible to the right of the sternum where dulness on percussion extended out 3.5 cm. from the right margin of the sternum. Diagnosis: Fibrous retraction of the heart. The sputum was blood tinged. A blood culture taken on this date was reported as sterile after three days' incubation.

On July 6 the patient had a severe chill lasting one half hour, vomiting during and after the chill. He complained of severe pain in the left side of

the chest. The temperature was 103° F.; pulse 88. Dulness was elicited over the left upper lobe anteriorly and posteriorly. Bronchial breathing and bronchophony were heard over the same area. The white blood count was 40,800; polymorphonuclears 89 per cent.; lymphocytes 11 per cent. Diagnosis: Lobar pneumonia (left upper lobe).

The following day the temperature was again normal. About three weeks later the patient had several distinct chills over a period of four hours, after which he felt weak. The spleen was palpable. The heart sounds were of poor quality, rate 100; sinus rhythm; the blood pressure was 98 systolic, 70 diastolic. Quinine was given, the signs and symptoms being suspicious of a malarial flare-up.

On August 8 another blood culture was reported as being sterile. The urine showed a few white blood cells and a few granular casts. An *x*-ray picture taken about this time showed partial consolidation in the basal and peripheral portions of the right upper lobe. The remainder of the lobe showed evidence of marked interstitial changes with a moderate degree of bronchiectasia. There were also interstitial changes in the right lower lobe. Moderate dilatation of the aorta was noted. *X*-ray diagnosis: Interstitial pneumonia, multiple abscesses, fibrosis, aortitis.

On August 11 the patient left the hospital against the advice of the physicians. In a little over two weeks he was readmitted, complaining of bloody and purulent sputum; pain in the left shoulder; chills, fever, sweats; weakness and loss of weight. The temperature was 101° F.; pulse 110, respirations 28. Examination showed a man who appeared chronically ill, with pallid and drawn face, perspiring profusely. The sputum was described as purulent and tinged with blood. Percussion gave marked dulness over the right upper chest posteriorly with broncho-vesicular breathing and amphoric breath and voice sounds over the apex. Tactile fremitus was increased. Over the right upper chest anteriorly the percussion note was suggestive of cracked-pot resonance, with amphoric voice and whisper. Moist râles were heard in the third right interspace. Percussion at this point was painful. Breath sounds were increased over the left chest.

The left border of the heart percussed 6 cm. from the mid-line in the sixth interspace. The heart sounds were muffled, of poor quality, and sinus arrhythmia was present. The rate was 84; no definite murmurs were localized; sounds at base were distant. The spleen was palpable. The liver margin palpated 7 cm. below the ensiform. The left shoulder joint was enlarged, painful, and felt hot. The white blood count was 11,000 with 74 per cent. polymorphonuclears and 21 per cent. lymphocytes. The red blood count showed a slight anemia—3,800,000 cells with 75 per cent. hemoglobin. Diagnosis: Abscess of the right upper lobe with cavitation (post-pneumonic); septic arthritis of the left shoulder joint; retraction of the heart to the right.

About a month later an *x*-ray showed a moderate amount of fibrosis and bronchiectatic cavity formation of almost the entire right lung. There was evidence of resolving pneumonia of the central portion of the left lower lobe with interstitial changes in the remainder of the lobe. There was slight retraction of the heart and of the trachea to the right due to fibrosis in the right

lung. X-ray diagnosis: Bronchiectasia, right lung; resolving broncho-pneumonia, left lower lobe.



FIG. 1.

On September 28 another x-ray report stated that there was a partial pneumo-thorax of the right pleural cavity (an artificial pneumo-thorax having been performed in the interval) producing about ten per cent. collapse of the lower lobe. There were several adhesions between the visceral and parietal pleuræ and also diaphragmatic adhesions to the right lower lobe.

On October 4 a large hemorrhagic rash was seen over the left thigh, hip and back. A week later a blood culture, taken on the 8th, was positive for *Streptococcus viridans*.

On October 13 the patient felt weak and asked continually for another artificial pneumo-thorax. The pulse was small and weak; rate 96. The day before his death the respirations were 30, pulse small and thready, rate 120. The patient died on October 16, five months after his first admission.

Autopsy was performed two hours post-mortem. The precordial area

was small, the left lung overlapping it for a considerable distance. The subepicardial fat over the right ventricle was yellowish brown in color, of jelly-like consistency and serous fluid escaped on sectioning it. The right auricle was distended. On opening it a large, pinkish-green, polypoid mass, measuring about $2 \times 4 \times 6$ cm., was present, bulging into the auricular cavity. The right atrio-ventricular orifice was practically occluded. The vegetation was covered here and there with patches of clotted blood, but otherwise it was quite smooth. The mass was situated on the anterior cusp of the tricuspid valve and was firmly adherent to it. The three cusps, which were greenish in color, were so welded together and thickened that they were practically indistinguishable one from the other. The chordæ tendinæ were thickened and shortened. The apex of the left ventricle presented a small clot of blood which was adherent to the columnæ carnæ, and on removal left a roughened muscular surface. The remaining heart valves were normal. The coronaries showed no lesion. The aorta was normal.

Anatomical diagnosis: Primary polypoid thrombo-endocarditis of the tricuspid valve; obliterative pleuritis (right upper lobe); chronic interstitial pneumonia (right upper lobe); chronic caseous tuberculosis (localized, right upper lobe); compression atelectasis (right lower lobe); lobular pneumonia (left lung); left hydrothorax; chronic septic splenitis; petechial hemorrhages in the mesentery, omentum and kidneys; acute parenchymatous nephritis; subcutaneous hemorrhages; subacute bacterial endocarditis.

Bacteriological examination: Showed small, gram-positive streptococci in pairs and short chains in a smear made by crushing a piece of vegetation from the tricuspid valve.

Microscopic examination: Heart—1. Section of the vegetation showed that it was composed of hyaline structureless material and fibrin. Gram-Weigert stain showed the periphery of the vegetation to be filled with innumerable, small, gram-positive streptococci, which appeared singly, in pairs and in chains. The interior portion of the thrombus showed no organisms.

2. Section of apex of right ventricular wall showed a large subendothelial collection of leucocytes, which infiltrated between the scanty muscle fibers, most of which had been replaced by fibrous tissue. This exudate was made up of polymorphonuclear leucocytes, lymphocytes, endothelial and plasma cells. The muscle at a distance from this lesion appeared fairly normal. Gram-Weigert stain of a section taken from the same portion of the heart demonstrated in the affected area organisms identical with those found in the vegetation.

3. Sections of the kidney showed that the lining membrane of the capsules of many of the glomeruli was proliferated, swollen and in some cases desquamated. Other glomeruli showed fibrin thrombi in the capillary tufts. In still others the capillary tufts were intensely congested and leucocytes were seen in the capsular space and beneath the epithelial lining of the capsule. The tubules presented no marked changes except that some of them contained leucocytes and red cells. The vessels of the organs had moderately thickened walls.

At Guy's Hospital over a space of forty-six years (1860-1906), during which time twenty-one thousand autopsies were

performed, thirty-five cases of infective endocarditis of the tricuspid valve were encountered. Of these, twelve showed involvement of the tricuspid only. These figures are proportionate to those of Bellevue Hospital, namely about one case of primary tricuspid endocarditis to every 1,750 autopsies. In the Gulstonian Lectures of 1885, Osler analyzed 209 cases of endocarditis and found the tricuspid valve involved alone in only five instances. In thirty-four cases of so-called subacute bacterial endocarditis studied by Libman which came to autopsy, not one instance of tricuspid involvement was noted.

The case just presented was a male fifty-five years of age. The five cases reported by St. George ranged from twelve to sixty-eight years of age; males predominated. The majority of cases reported in the Guy's Hospital statistics were between the ages of ten and forty years; the number of male and female cases was about equal. Infants and children seem to be almost exempt from endocarditis other than that due to acute rheumatic fever and chorea. Congenital (fetal) endocarditis on the other hand is not an infrequent finding and is almost always confined to the right side of the heart. In 237 cases of congenital endocarditis, Rauchfuss found right-sided lesions in 192. According to Osler, this relative frequency of endocarditis on the right side is probably due to greater tension which has to be borne during fetal life in contradistinction to the lessened strain put upon the tricuspid valves in adult life.

As regards the causative agents in these cases of tricuspid endocarditis, the findings are variable. In two of the cases recorded by St. George, blood cultures were taken, one showing the presence of *Staphylococcus aureus*, the other *Pneumococcus*. Cultures were made from a lung infarct and a heart valve in a third case and both showed *Streptococcus hemolyticus* in pure culture. In the case presented here the third blood culture was positive for *Streptococcus viridans* of Schottmueller, as was also the smear from the vegetation.

To the above-mentioned organisms, namely the *Staphylococcus*, *Pneumococcus* and the two varieties of *Streptococcus*, may be

added the *Gonococcus* and the Influenza bacillus, as being important causes of malignant endocarditis. The term "malignant" as first employed by Osler in describing cases of acute endocarditis is clinical rather than anatomical, and refers to cases with severe constitutional disturbances and extensive valve lesions, whether ulcerative or vegetative lesions. Pneumonia heads the list of all diseases complicated by severe endocarditis (Osler). G. W. Norris states that lesions of the right heart are more common in this form than in other varieties of endocarditis. In 141 cases of endocarditis in pneumonia, Preble encountered twelve, or 8.5 per cent., which involved the tricuspid valve alone.

The case presented to-night illustrates the type of endocarditis produced by the *Streptococcus viridans* of Schottmueller or the endocarditis coccus of Libman. The disease is comparatively slow in its progress; of about five months' duration in our case and from four months to one year or even one and one half years in forty-five cases studied by Libman. As MacCallum states, the heart valves are subject to remissions or periods of partial healing, but the disease nevertheless goes on to the death of the patient.

Vegetations due to the *Streptococcus* are apt to be large and to grow rapidly. Occasionally they are so massive, as typified in the case here presented, as practically to occlude the valvular orifice. It is stated (Norris, G. W.) that vegetations of considerable size are more apt to produce insufficiency than stenosis. In the majority of the Guy's Hospital cases of tricuspid endocarditis the valves were incompetent, yet in only five cases was a systolic tricuspid murmur noted; one case gave a diastolic murmur. No definite murmurs were noted in the case here presented.

The general symptoms of tricuspid endocarditis are the same as those present in any case of malignant or subacute bacterial endocarditis, namely fever, with or without chills, progressive weakness, enlarged spleen, hematuria, petechiæ and painful cutaneous nodules.

Since the diagnosis of tricuspid endocarditis is usually dependent upon the presence of insufficiency or stenosis of the valve,

reference is made to the extensive discussion of "Tricuspid Stenosis and Tricuspid Insufficiency," by Young and Cotter, and to St. George's paper on "Malignant Tricuspid Endocarditis" (see References).

The striking features about the case presented were:

1. Its likeness to malaria as shown by the chills, fevers and sweats.
2. The lung changes which accompanied the heart lesion.
3. The absence of any definite cardiac symptoms, dyspnoea or edema never having been complained of.
4. The similarity of the pathological lesion in the kidneys to that found in subacute bacterial endocarditis as described by Baehr before this Society in 1911.
5. The massive vegetation on the tricuspid valve with no involvement of any of the other heart valves.

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Discussion:

DR. ST. GEORGE: The clinicians' diagnosis is not always confirmed at autopsy. The case I had in the Army was that of a negro who was seen a great number of times on the ward, as he ran a chronic course. All the attention was focussed on the lung condition; he had, it was thought, an influenzal pneumonia with empyema; he was operated on and nothing was found. At autopsy, however, the endocarditis was encountered. The diagnosis of the condition is, of course, very difficult. In this case there were no heart murmurs encountered. The above patient and the records in the Bellevue cases differ from the case presented tonight in that all had heart murmurs, only they were not properly interpreted. I think that this case opens the question as to whether the lung condition was primary and the endocarditis merely a

terminal infection, or whether the endocarditis produced the lung symptoms, as is generally thought to be the case. In this particular instance there was a good deal of fibrosis through the lung, and I doubt whether one could justifiably attribute the lung symptoms to the heart. It is quite possible that he had pneumonia and that the heart affection was simply a terminal event.

HETEROGENEOUS TISSUES IN FEMALE SEXUAL ORGANS

EMIL SCHWARZ, M.D.

The few cases to be demonstrated to-night require for their explanation certain embryological data. The gross specimen is an intra-mural tumor of the corpus uteri weighing twelve and a half pounds, well defined against the myometrium. It is composed almost exclusively of a yellow, very soft tissue with occasional islands of a greyish firm tissue, which also prevails in the periphery and fuses with the yellow structures. The growth is plainly a lipo-myoma, which on microscopical examination shows the typical appearance of this rather infrequent tumor. Up to 1908 there were seventeen cases reported, and one recent case in 1920 was described by Williamson and Brockman in the *Proceedings of the Royal Society of Medicine*, London, which had been removed sixty years before by Sir James Paget. The lipoblasts described by several authors were present in the reticulum, as well as in the smooth muscle islands. Besides that numerous mononuclear eosinophilic cells and large cells with fine delta granulations, staining well with Dahlia, can be seen in sections. In the sixth edition of Killiker's Histology there is a reference to these cells which according to the author are present in the tunica dartos of the testicle, and which he assumes to be predecessors of the lipoblasts. This fast growing tumor, which is entirely benign, seems to present all the stages of the formation of fat cells. In order to explain this and some of the following cases, I am showing on the screen a 1.38 mm. embryo of Pfannenstiel-Kroemer, and a 2.8 mm. embryo of my collection. The differentiation taking place in the nephrogenic cord between these

two embryos indicates that mesenchymal persistent tumors, as well as "faulty mixtures and aberrations," must occur after the first shown embryo and before the second is developed.

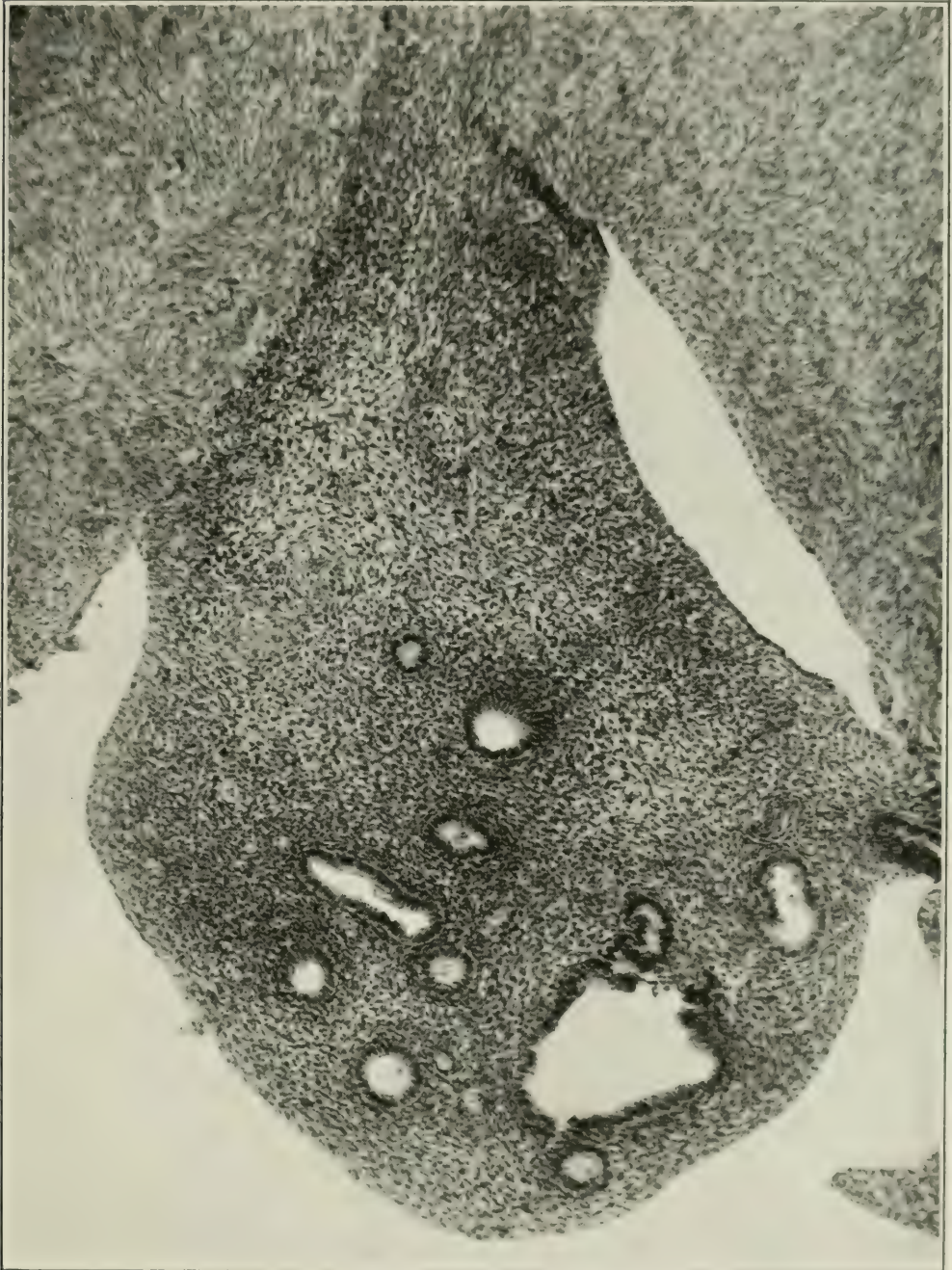


FIG. 1.

I am also demonstrating a cyst 2.5 cm. in diameter, developing laterally of the introitus vaginæ at the level of the hymen. The

cyst is lined with one or two layers of a high columnar ciliated epithelium. The site of the epithelial lining and the exclusion of other possibilities lead to the assumption of a cyst of Gartner's duct.

Microscopically entirely different, but histogenetically identical, is another specimen showing numerous glandular lumina which are located in the stroma of the cervix uteri near the attachment of the broad ligament. These glands are lined with a low cuboidal epithelium easily distinguished from cervical glands. Although resembling epoophoron tubules they are apparently cross sections of a branched ampulla of Gartner's duct, since remnants of Wolffian body cannot occur below the second crossing of the latter and the tubal portion of Mueller's duct.

A section which I am at a loss to explain shows on the convexity of an otherwise normal, perfectly free ovary a small growth arising from a groove in the albuginea of the ovary. The cytogenic stroma of this funnel-shaped growth, which measured 1.5 mm. in diameter, contained numerous glands of the corpus type, and sent a short processus into the ovarian stroma (Fig. 1).

PURE CULTURE OF *B. INFLUENZÆ* FROM PELVIC ABSCESS

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(*From the Pathological Laboratory of St. Luke's Hospital, F. C. Wood, Director*)

The influenza bacillus of Pfeiffer is commonly associated with diseases of the respiratory system, including the nasal passages and the accessory sinuses. It may be the specific etiologic factor in some of these conditions, while in others only a secondary invader. Its primary importance as the cause of epidemic influenza, first postulated by Pfeiffer, has been questioned in the last few years by various investigators. Some would relegate this organism to a secondary rôle in the disease. Regardless of whether or not it is the cause of true influenza, it is frequently

associated with other acute infectious diseases such as measles, scarlet fever, whooping cough, chickenpox, and diphtheria, where it occasionally may be present in the blood stream. The respiratory system harbours it in the more chronic conditions of the lungs, as pulmonary tuberculosis, bronchitis, bronchiectatic cavities, while empyema exudates may contain the organism. It has been recovered from the central nervous system in cases of cerebrospinal meningitis and more rarely brain abscess, while the special sense organs show involvement as in otitis media and possible extension into the mastoid cells. Acute contagious conjunctivitis ("pink eye") falls in this class, and may be the result of the Koch-Weeks bacillus, which some competent bacteriologists consider identical with the influenza bacillus. In the gastrointestinal tract it has been recovered repeatedly from the mouth, tonsils, and throat. It is often found in the accessory nasal sinuses. Further, an acute and chronic gall-bladder infection may be due to this bacillus, and appendicitis and peritonitis may develop. Frequently the influenza bacillus in these conditions is associated with other pus-forming organisms.

Septicemia with recovery of the organism was observed shortly after the discovery of the bacillus, and endocarditis with vegetations in which influenza-like organisms have been found demonstrates its presence in the cardio-vascular system. The genito-urinary tract is not exempt, for cases of cystitis have shown the influenza bacillus to be present in culture.

From this brief survey one can see that the organism has the ability to invade and establish itself, either primarily or secondarily, with the ancillary organisms—the pneumococcus and the streptococcus—in practically all regions of the body. It would appear that even in inter-epidemic periods this organism is always present to a certain extent among individuals as carriers in thickly populated areas and cities, and may give rise to sporadic outbreaks, or isolated cases of infection. Probably the true nature of some of these infections is not recognized clinically, or laboratory examinations have not been undertaken as an aid to diagnosis. Recently, the authors had an opportunity to study

such a case, through the courtesy and helpful cooperation of Dr. E. D. Truesdell, Assistant Attending Surgeon of St. Luke's Hospital, to whom we are further indebted for clinical and operative notes.

In a brief survey of the literature, we have found no report of a similar condition, therefore we take the occasion to present to this Society the history of the case with the laboratory findings:

Case No. 162,734. Admitted to St. Luke's Hospital, November 2, 1922. The patient was a young woman, aged twenty-eight years, and of American nationality.

Marital history shows her to have been married at the age of twenty. There had been one pregnancy, the child a boy now seven years of age. She has been a widow for three years.

Past history discloses the following facts: She suffered from the usual infectious diseases of childhood. Three years ago, during the influenza epidemic, she had an illness characterized by chills, fever and cough which kept her in bed for a week. Her physician pronounced it a "heavy cold." Gastro-intestinal history states that she is subject to constipation of the bowels and has never had attacks of diarrhœa until one or two days before admission to the hospital. At this time there were seven movements daily. There have been no recurrent colds or attacks of bronchitis, although she suffers from the usual and occasional "cold in the head." She gives no history suggestive of chronic sinus involvement, and there has never been an acute or chronic vaginal discharge.

Present illness: The onset occurred one week before admission, the patient being confined to bed with pain in the lower half of the abdomen and in the back, cramp-like in character, of half hour's duration, and reappearing at three- to four-hour intervals. As in the other attacks she felt feverish. There was no nausea or vomiting at any time during the illness. The bowels were constipated except for the moderate diarrhœa just before coming to the hospital which was mentioned above. The patient had had two similar attacks of less severity and short duration (twenty-four hours) in the preceding March and August. She was confined to bed one day in each instance.

On admission the patient had a temperature by mouth of 99.8° F., which rose to 100.4° on the following day.

Physical examination: The patient appeared well nourished, with good color, showing no evidence of acute sickness. There was no rigidity of the abdomen and no masses were felt. Upon deep pressure there was moderate tenderness in each groin. The uterus could not be felt anteriorly in pelvic examination, but in the posterior fornix a mass of moderate size was found which was moderately tender. A pre-operative diagnosis was made of retroflexed and retroverted uterus, chronic salpingitis with pelvic adhesions.

Operation: Upon opening the abdomen the body of the uterus was found to be in the normal position. The pelvis was occupied by a mass composed of adherent sigmoid and small bowel. Upon separation of the adhesions yel-

lowish-green, odorless, thin pus was liberated. Culture material was taken upon sterile surgical swabs and sent to the Bacteriological Laboratory for examination. Both tubes were found to be red and congested in appearance, but not thickened; the outer extremities were not occluded. The ovaries appeared normal. The adhesions were separated sufficiently for evacuation of the pus and the insertion of a drain. Attention was then directed toward the appendix, where no adhesions were observed in the right iliac fossa, either of the omentum or small bowel, to or about the cecum. Upon elevation of the cecum the appendix was found plastered to the posterior surface of that structure and somewhat buried in it, and adherent to the mesenteric attachments of that region. Upon attempting to free the appendix, about a dram of pus similar to that found in the pelvis was liberated. The appendix was red, slightly swollen, but without perforation, gangrene, or appearance to explain the small retrocecal appendix abscess. The appendix was removed and a drain placed in the lower angle of the abdominal wound reaching to the bottom of the pelvis and the remainder of the wound closed.

Post-operative diagnosis: Pelvic abscess, retrocecal abscess about appendix; secondary subacute appendicitis.

Laboratory examinations: A full blood count made on the day following admission showed red blood cells 3,800,000, hemoglobin 84 per cent.; white blood cells 14,000; polynuclear leucocytes 88; lymphocytes 12.

The Wassermann reaction was negative.

Bacteriological examination: Cultures were made of pus upon dextrose agar slant, dextrose broth, and human blood agar plate. No growth developed after the usual incubation on either the dextrose agar slant or the broth, but upon the blood agar plate small colonies appeared, which were found to be composed of small Gram-negative bacillary forms morphologically characteristic of the influenza bacillus. Fishings made from these colonies transplanted to dextrose agar slants and broth failed to develop a growth after several days' incubation. On the other hand, similar transplants upon five per cent. human blood agar slants showed typical growths of the influenza organism on incubation. Transplants from these cultures again failed to develop growth when transplanted to dextrose broth or carried through a series of transplants to dextrose agar slants. The organism was reported as *B. influenza* in pure culture.

Pathological examination of appendix (Dr. L. C. Knox).

Diagnosis: Subacute appendicitis.

Macroscopic examination: Specimen consists of an appendix 4 cm. in length. It has been opened in the operating room. The peritoneal covering has lost its luster, but is not markedly injected. The mucosa appears thickened and there are small hemorrhages in the submucosa, but the markings are fairly distinct throughout.

Microscopic examination: Section of the appendix shows a subacute infectious process which has involved all the coats, but which shows evidence of considerable healing. There is no necrosis. The exudate has been largely absorbed, although there is still increased vascularity throughout, edema, and productive areas in the mucosa and submucosa. Both of these coats contain

fresh hemorrhages and their capillaries contain unusual numbers of polynuclear cells. There are collections of round cells in the perivascular spaces of the muscle coats and in the subserous reticular tissue. Since all the coats are affected, the process appears to have originated within the appendix, rather than to have been an extension from the pelvic inflammation.

Subsequent course: The convalescence was uneventful, the patient having left the hospital within two weeks with a small sinus and slight discharge.

From the bacteriological standpoint this case is of interest owing to the unusual finding of *B. influenza* in pure culture of pus from a pelvic abscess. The original source of the infection and the route of invasion of the pelvis are matters subject only to speculation, since none of the possible explanations can be proved. No primary focus of infection in the patient, such as a pulmonary condition (recent influenza, bronchitis, etc.) or accessory nasal sinus involvement, could be found. There were no gastrointestinal disturbances, other than the three attacks during the last seven to eight months which might indicate a mild appendix involvement. Unfortunately the appendix after removal at operation was not sent to the Bacteriological Laboratory for cultural examinations; therefore the question of whether it showed the presence of *B. influenza* cannot be answered. Presuming that the influenza bacillus was present and had broken through the wall of the appendix, a mixed infection with intestinal types of organisms might have been expected. Another possible route of invasion to the peritoneum might occur through the vagina, uterus and tubes, although the history offered no evidence of any infection of the genito-urinary tract. Among other sources of infection the blood stream or the lymphatic system might possibly carry the organism from a focus such as the tonsils, or from the urinary tract, and deposit it in the region where found. The question whether the infection in the pelvis was primary or secondary to some other focus in the body still remains open. If the latter, perhaps the appendix should be given first consideration.

A CASE OF SULPHEMOGLOBINEMIA

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In 1910 Clarke and Curtis¹ described the first case of sulphemoglobinemia recognized in America, but no other instances of the affection were reported in this country till 1921. Mason and Conroy² in that year published a typical case, stating that it was the thirteenth so far put on record. The present case of sulphemoglobinemia was seen and studied by the present writers in 1916, making it the fourteenth example of the condition to be reported, and the second of the three so far found in this country.

The patient, who was first seen on February 28, 1916, was a young man whose appearance was remarkable in that his lips and ears were distinctly blue and his features of a livid pallor. He stated that for the past three weeks he had suffered from vertigo and fainting attacks, a severe attack occurring on the preceding day. His employment was in a chemical factory in which he was engaged in the production of a photographic developer containing para-amido-phenol, made by the electrolysis of nitrobenzene in a concentrated sulphuric acid solution, lead electrodes being used. The skin of his hands was thickened, rough and fissured. No drugs had been taken except some tablets of sulphur and cream of tartar. He had been told by a physician that he was suffering from lead poisoning.

Examination of the heart and lungs revealed no abnormalities and the routine examination of the urine was negative. Further tests proved the absence of phenol, urobilin, urobilinogen, or blood pigments. The blood examination showed 5,200,000 red cells, hemoglobin 80 per cent., 10,000 leucocytes, with polynuclears 76 per cent., lymphocytes 22 per cent.; and eosinophiles 2 per cent. The stained smear showed no basophilic stippling of the red cells, nor anything else of note. The Wassermann reaction was negative.

In the absence of any pulmonary or cardiac condition to account for the cyanosis the possibility of poisoning by some of the agents with which his occupation brought him in contact suggested itself and the blood was examined with the spectroscope. An absorption band was visible between the C and D lines, in about the position of the characteristic band of methemoglobin, but as one of the authors had seen and studied Clarke's patient with sulphemoglobinemia, who for a time was under investigation at St. Luke's Hospital, it seemed possible that this was an instance of the same condition, and further tests were performed. Comparison of the band in the patient's blood with the spectrum of artificially prepared methemoglobin showed that it was further to the right than the band of the latter. The addition of ammonium sulphide

to a solution of methemoglobin causes the band of this substance to disappear, while the spectrum of sulphhemoglobin is unaffected by this treatment. The test confirmed the identity of the pigment in the patient's blood, and in order to complete the demonstration synthetic sulphhemoglobin was prepared, and its spectrum was found to be absolutely coincident with that obtained from the patient's blood. In making these observations a comparison spectroscope was used, making it possible to note with absolute accuracy the slightest differences in the position of the absorption bands.

Tests made on the serum showed that it contained no sulphhemoglobin, but that a reducing substance was present. Tests for nitrites were negative in the blood, the serum, and the urine, but positive in the saliva.

Two weeks later the patient's appearance had improved and his symptoms had almost entirely disappeared, but the sulphhemoglobin was still present in marked amount.

On March 22 he reported that he had been able to go back to work, and though sulphhemoglobin was still easily demonstrable it was less in amount. During the following weeks he was seen repeatedly and the sulphhemoglobin did not entirely disappear from the blood till June 26, though the serum still showed a slight reducing action.

Wallis³ ascribed etiologic significance to the presence of a Gram-negative, cocco-bacillary organism with reducing properties which he found in the mouths of five English patients suffering from sulphhemoglobinemia, and an attempt was made to confirm this observation in our case. Cultures made following the methods used by Wallis were negative as far as any forms corresponding to the "nitroso-bacillus" were concerned, and blood cultures made under both aerobic and anaerobic conditions were also negative.

Cyanosis may be produced by overdoses of various drugs, especially acetanilid, phenacetin, trional, sulphonal, potassium chlorate, nitrites and nitrobenzol; not through cardiac depression, as often believed, but through the formation of methemoglobin. In a few reported instances methemoglobinemia has been observed though no external cause for its production could be discovered and to this condition the name of enterogenous or idiopathic cyanosis has been applied. These patients all suffered from severe diarrhea, were markedly cyanosed, and as nitrites were found in the blood by von der Bergh and Gutterink,⁴ it has been believed that the absorption of nitrites from the intestine was responsible for the production of the altered blood pigment. In 1906 von der

Bergh reported four other cases, however, equally of unknown etiology and resembling the former group except that the patients were all constipated. Careful study of the blood with the spectroscope showed that the spectrum given was not that of methemoglobin but that of sulphhemoglobin. It was also found that while temporary disappearance of the methemoglobinemia followed putting a patient on an exclusive milk diet for forty-eight hours, no change occurred under these conditions in the sulphhemoglobinemia cases. Several other authors have described similar cases, three of which have been recognized in this country, the first discovered by T. Wood Clarke in 1910 and reported by him after study in St. Luke's Hospital, the present case observed in 1916, and that of Mason and Conroy seen in 1921. The latter case and our own are the only instances in which the patients have been adult males, all the others being females except one of von der Bergh's, who was a young boy suffering from a congenital stricture of the rectum and a rectovesical fistula.

From the studies of Clarke and Hurtley⁵ it appears that the presence of reducing substances greatly facilitates the production of sulphhemoglobin from even minute traces of sulphuretted hydrogen. Wallis believed he had found the source of such a reducing substance, needed to aid in the formation of sulphhemoglobin from the sulphuretted hydrogen of the intestine, in the isolation of a "nitroso-bacillus" in the saliva. This could not be found in our case, and similar failures are reported by Long and Spriggs, and also by Mason and Conroy.

The manner in which the formation of the abnormal blood pigment is brought about is still unknown, but it appears that two factors must gain access to the blood, sulphuretted hydrogen and a reducing substance, and in most cases it is probable that the former originates in the bowel. In our patient's case several significant features are to be noted. Unlike most of the reported patients he had not been a sufferer from constipation, and his blood affection developed in connection with two special circumstances. One was that he had been taking a preparation containing sulphur, and the other that the sulphhemoglobinemia de-

veloped rather quickly at a time when he was showing the evidences of nitrobenzol poisoning in the condition of his fissured, scaly and itching hands. After he had stopped taking the sulphur, and had been protected from the action of the nitrobenzol by absence from his occupation and later by wearing rubber gloves when at work, the sulphemoglobinemia disappeared, a behavior very different from what has generally been noted, as in most cases the condition has proved very intractable to treatment. It is suggested that in our case the sulphemoglobinemia was of a different type from that heretofore described, and that in this case the combination of the two factors of the ingestion of sulphur, and the absorption of nitrobenzol brought about the formation of the abnormal blood pigment.

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CONGENITAL ABSENCE OF GALL BLADDER

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Fifty-seven years ago Dr. Henry B. Sands showed before this Society a rather infrequent malformation consisting in the absence of the gall bladder and therefore the demonstration of a similar specimen may not be without interest, especially as none have been shown here in this interval.

The French anatomists have given more attention to the subject than others, and have said that such an omission is not really infrequent but their literature reveals not more than a score

of cases. In the *Transactions of the Philosophical Society of London* for the year 1701 L'Emery is said by Eschner to have described the liver and hepatic ducts of an infant without a trace of a gall bladder in the specimen. References are made in the literature to about forty other instances of this defect, although it is possible that a few of these are described twice, several of the specimens in the anatomical museums of the London hospitals having been referred to a number of times. Many of the references cannot be verified. Kehr, summarizing the subject, mentions six cases in infants with other malformation and thirteen cases in adults, two associated with malformation of the liver.

Abstracts of the available cases are as follows:

1. Huber, 1744. Author showed liver of woman 60 years of age with no gall bladder. Hepatic ducts were much dilated.

2. Sir E. Home, 1813. Infant a few months of age. Appeared fairly healthy at birth, took feedings readily but became emaciated, skin darkened in color, and all subcutaneous fat disappeared. At autopsy no trace of gall bladder was found.

3. Wilson (cited by Canton). Described a liver with a shallow groove in its substance replacing the gall bladder. The hepatic ducts were normal, the common duct was dilated, and its mucosa furrowed, resembling that of the gall bladder.

4. Canton, 1847. The author autopsied the body of a woman 65 years of age who had died of cerebral hemorrhage, and found the liver two thirds the normal size, the gall bladder missing, the hepatic ducts normal in position and calibre; but the common duct was twice normal size and its mucosa was rough and furrowed. The cystic artery was absent.

5. Thomas, 1848. An infant five months of age had been jaundiced from its second day, had vomited almost continuously; the stools were white, the extremities edematous, and the abdomen contained bile-tinged fluid. There was no gall bladder and no extra-hepatic ducts affording any drainage whatever.

6. Harle, 1856. Brief mention was made of a liver found at autopsy, colored dark green and with no trace of a gall bladder and no cystic duct.

7. Simpson, 1861. The writer attended a new-born child suffering from diffuse lesions of the skin at first thought to be sclerema but these later suppurated and were found to be infectious. The infant vomited continuously and died at the age of four weeks of peritonitis. There was no gall bladder and no fossa in the liver but the other ducts were normal.

8. Patterson, 1864. At autopsy on the body of a man 35 years of age who died from asthma, the liver was found four times normal size, soft and fatty with no trace of a gall bladder.

9. Sands, 1865. The writer demonstrated before the New York Patho-

logical Society the liver of a male who had died of tuberculosis at the age of 20. There was no quadrate lobe, no fissure for the gall bladder, and the hepatic ducts were somewhat dilated.

10. Pozzi, 1872. This writer described a monster, not viable, with hernia of the diaphragm and several other gross anatomical defects, among them complete absence of the gall bladder and all extrahepatic ducts. The similar case of Porak is cited.

11. Lynch, 1875. This case also occurred in an infant, jaundiced since its second day and dying in the eleventh week. There were multiple hemorrhagic cutaneous lesions; the stools were white, and there was constant pain and tenderness in the epigastrium. The liver was found to be large, the hepatic ducts small and the gall bladder missing. All tissues were intensely jaundiced. The common duct was not dilated. The pancreas was apparently normal.

12. Rambault and Schachman, 1882. A liver was described without gall bladder but with normal hepatic ducts. The conditions occurred in a paretic and had apparently caused no symptoms.

13. Hochstetter, 1886. The liver of an infant who had died at the age of eight days was shown. The right lobe was very large, the quadrate lobe absent and the left small. The gall bladder was missing and the ductus choledochus, placed slightly further than usual to the left, entered the duodenum at a point higher than normal.

14. Eschner, 1894. Twelve cases of missing gall bladder were enumerated by this writer, but many of them he himself regarded as probably resulting from inflammatory processes and not a primary agenesis. The author's own case was found in the body of a child two years of age. Death was due to pneumonia. The liver, otherwise normal, possessed no gall bladder.

15. Kirmisson et Herbert, 1903. The case occurred in a phocomelus infant one month old who died of a pulmonary infection. The child had been jaundiced since its third day. The liver was hard, green, and had no gall bladder as well as no ducts connecting it with the intestinal tract.

16. Blakeway, 1912. At autopsy on the body of a newly born infant several defects were found—absence of the gall bladder, non-development of the corpus and cauda of the pancreas, and a blind sac at the end of the rectum, this cloacal pouch communicating with the prostatic urethra.

17. Torrence, 1920. This surgeon has been apparently the only one to record the complete absence of a gall bladder discovered in the course of a laparotomy. The patient was a male thirty-eight years of age, upon whom appendectomy had been performed. The common duct appeared normal.

Possibly the specimens mentioned by Mayo-Robson, Walton, Latham, and Thursfield are the same as those described elsewhere.

Interest in the subject centers in the fact that the omission represents a definite congenital defect with which is more than likely to be associated some other defect. Of the sixteen cases

regarding which the facts are at hand, other gross abnormalities have accompanied them in three instances and in four infants there have been no means of communication with the intestinal tract. Mayo-Robson has stated that life could exist for months in this extraordinary condition, referring perhaps to the case of Cnopf (cited by Kehr), who observed an infant with no ducts or gall bladder, but who survived for twenty-three weeks. It will be noted that in the case of Thomas the infant lived for five months, while the one observed by Kermisson and Herbert lived for one month. Jaundice and metabolic disturbances were clinically prominent features of each case, but death was directly due to infection.

Since ten of the cases are known to have died in infancy, it is probable that in these there were also other serious defects, anatomical or functional. If, on the other hand, the ducts are of normal calibre and distribution, the absence of the gall bladder from birth may cause even less disturbance of function than follows the surgical removal of the viscus.

The question of compensatory dilatation of the common duct after cholecystectomy is by no means settled, although the opinion prevails that such will occur unless infection has altered the walls too extensively. It is therefore of interest to note that in only four of these cases has dilatation of the hepatic or common ducts been observed; and three of these occurred in adults not known to have suffered from any symptoms referable to the biliary tract. Dilatation of the ducts has never been seen in infants.

It is somewhat remarkable that, although there is no gall bladder in certain families of birds, of fish, some of the rodents, the deer, camel, rhinoceros, and elephant, important abnormalities in its development are so infrequent in man.

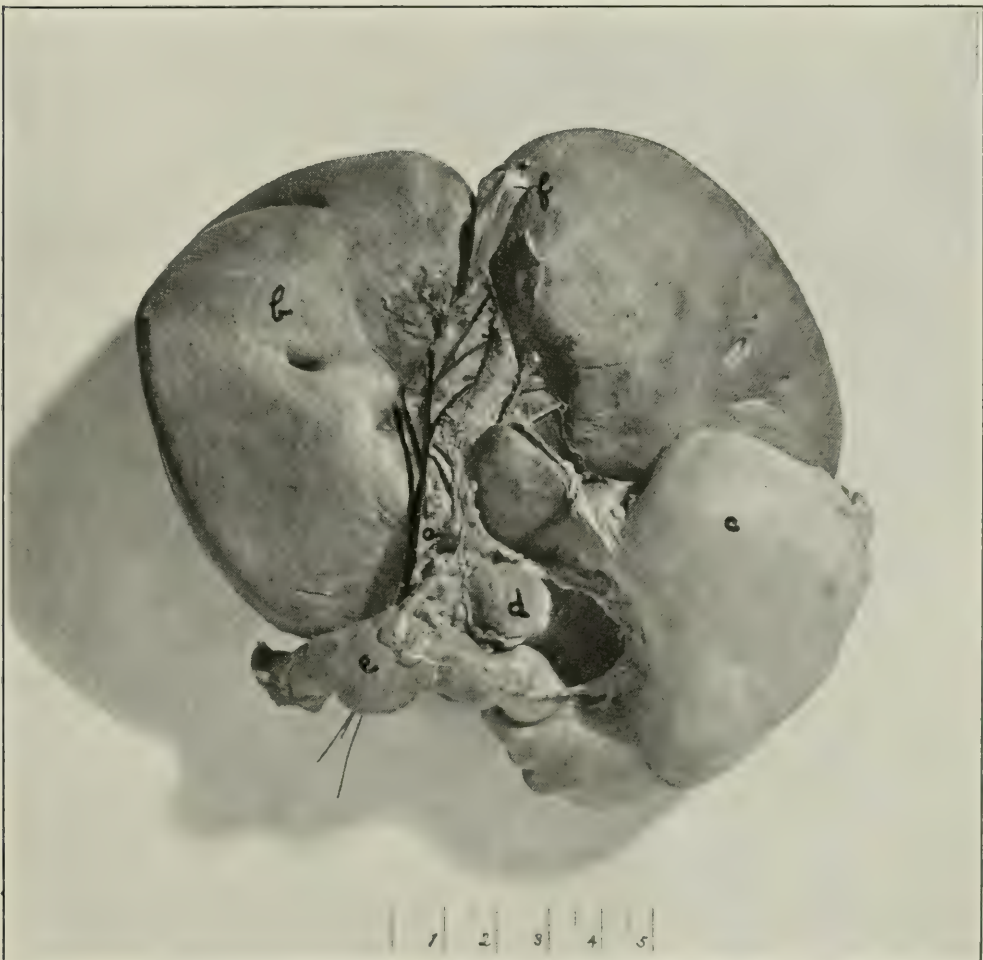
Dév  estimates that in infants two per cent. are totally intrahepatic, but that this condition is never found in adult life as all grades of covering of the viscus by the liver parenchyma are seen, and that there is a regular tendency of the liver cells to recede or atrophy and leave the serosa in contact with the viscus. Brewer found few anomalies in position in an anatomical study

of 100 cases, the commonest being the possession of a mesentery, but this was present in only five per cent. A true left-sided gall bladder with viscus and common ducts both to the left of the falciform ligament is said by Schachner to have been reported thirteen times without transposition of other viscera. Double gall bladders and double cystic ducts have been seen, but are extremely infrequent. Absence of the gall bladder of course necessitates some change in the blood vessels, but anomalies of these are much more frequent and more varied than those of the ducts. The cystic artery may be either absent or distributed to the parenchyma of the quadrate lobe. Unimportant variations in the lobulation of the liver have been frequent; a slight fossa may or may not be present, and therefore there may be no line of demarcation of the quadrate lobe, though the gland is otherwise normal.

It is of interest that no defects in the upper part of the head of the pancreas are described even in the cases in which the larger biliary ducts are absent. Developmentally the liver represents a diverticulum from the ventral side of the entoderm shortly beyond the stomach. Two portions, a cephalic, fairly solid portion, and a caudal hollow one, are early differentiated. The latter, the lumen of which is continuous with that of the duodenum, represents the gall bladder. By a constricting process the ductus choledochus and hepatic duct are formed and remain as the only connection which the cephalic portion or pars hepatica retains with the duodenum. The pars cystica in the meanwhile dilates to form the gall bladder and elongates to establish a cystic duct. One or possibly two ventral evaginations from the entoderm are the anlagen also of the head of the pancreas and appear at about the same time as the liver; therefore one might expect abnormalities of the one gland or its ducts to accompany those of the other. These two buds arise from the ductus choledochus, the left probably atrophying early, but the right eventually forms the duct of Wirsung and the ventral part, or head, of the pancreas. If, therefore, the head of the pancreas is normal while the common duct and gall bladder are absent, this defect is prob-

ably due to an early secondary atrophy of their anlagen. A dorsal bud which arises slightly caudal to the ventral one forms the head and tail of the pancreas and it is an interesting fact that in the case of Blakeway there was a defective budding in this region as well as in that of the ventral portion. The hind gut also was incomplete. Unfortunately all the instances of this rare lesion were reported before extensive microscopic sections were made, and we have no studies revealing the condition of the intra-hepatic bile radicles.

The specimen here shown was removed from the body of a female infant aged one year. The child was normally developed, and well nourished, had



Photograph of liver showing absence of gall bladder and distribution of bile ducts. *a*, common bile duct; *b*, liver; *c*, stomach; *d*, pancreas; *e*, duodenum; *f*, falciform ligament.

had an uneventful history with no record of illness until four days before her admission to the hospital when she had an attack of diarrhœa. The symptoms improved but after a week in the hospital she died rather suddenly.

At autopsy it was decided that death was due to a small patch of broncho-pneumonia and to an exudation of pus in the left pleura. This was small in quantity but widely distributed over the entire pleural surface. On lifting up the liver not a trace of gall bladder could be seen, nor any evidence of previous inflammation. The common duct is not dilated, the papilla of Vater normal in size and position. The hepatic ducts are somewhat anomalous as there are two small ducts from the right lobe which join the common trunk below the three which proceed from the left lobe. The hepatic artery and portal vein are normal. There is a slight groove in the liver marking the right margin of the quadrate lobe. The pancreas is normal. Other deformities or abnormalities were not found.

Microscopic sections of the liver show normal lobulations but unusually wide fibrous portal canals in which the bile ducts even at the periphery of the gland are much dilated and lined with tall columnar epithelium. There is no inflammatory lesion. The parenchyma shows a very severe grade of fatty infiltration as about half of each lobule stains heavily with Scharlach R, and the normal liver cells are here apparently entirely destroyed.

CONCLUSIONS

A case of congenital absence of the gall bladder in an infant is presented. No symptoms referable to this lack were observed during life.

The hepatic ducts in this instance have an anomalous distribution but neither they nor the common duct are dilated. The intrahepatic bile ducts are dilated and the liver shows widespread fatty infiltration.

Possibly forty other cases of this defect have been described, about half of them in infants.

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MITOCHONDRIA IN TUMORS

FRANCIS CARTER WOOD, M.D., AND ANGELA C. HARTMAN.

(From Columbia University, Institute of Cancer Research, F. C. Wood,
Director)

The motive for this study of mitochondria in tumors arose from a desire to obtain a method of determining the death of a cell after radiation. As you all know, it is perfectly easy to determine the death point of a mouse tumor by inoculating the tumor into another mouse and seeing whether the tumor grows or not, but it is not possible to determine the lethal dose in man without waiting until the patient either dies of the tumor or shows metastases. So this study was begun to attempt to obtain some means of estimating whether the cells of a human tumor have been killed by a given dose of radiation. If such a morphological criterion could be obtained it would be very easy to give accurate dosage to human tumors, for by excising a small piece after raying we could determine whether the cells were dead or not. If not, more *x*-ray might be given.

Evidently the first thing to do is to determine the normal mitochondrial morphology of the tumors used. The technique is rather laborious, and the demonstration of mitochondria is not

constant. They may be visible in certain groups of cells or in certain parts of the section, but occasionally the method fails in material in which we know there has been no error in technique. It has been said that in sarcomata in man the chondriosomes were usually in the form of rods, and in carcinomata they formed small granules, staining much less deeply than in sarcomata. That is not true of animal tumors, as you will see from the drawings, because the first specimen is a sarcoma, and the granules are exceedingly small. They lie outside of the division figures, and are distributed at random throughout the cell, and often collect at either end of the poles of the nucleus.

These drawings show tumors which have been rayed with large doses, and one of these immediately after the raying shows no change except possibly a slight change in the rods of the chondriosomes. The cells are swollen, an alteration in the cell probably due to changes in the cell membrane in those cells which have been killed. In other tumors it is not possible to tell that the tumor had been rayed at all. In other words, the chondriosomes were exactly what are considered normal. They were taken only twenty-four hours after the exposure. Such exposed tumor cells remain in a viable condition for six or eight days after the dose has been given, and then die. But a determination of the cell death within twenty-four or forty-eight hours would be a great advantage, because we cannot give a large pre-operative dose to a human tumor and permit the patient to wait until there is a deep burn. The tumor must be excised within forty-eight hours at most when such large doses are given, because otherwise serious pain and large sloughs will occur. So this mitochondria method, if it is to be of value, must give an answer within seventy-two hours at the outside. That sufficient morphological changes occur in mitochondria after a lethal dose of *x*-ray to permit of an estimation of the effectiveness of the application is, so far as our work has gone, doubtful.

HISTOLOGICAL STUDIES OF TUMOR CELLS AFTER X-RAY. I. PRELIMINARY REPORT ON THE MITOCHONDRIA AND DEGENERATION VACUOLES

R. E. PRIGOSEN, M.D.

*(From Columbia University, Institute of Cancer Research, F. C. Wood,
Director)*

The large and rapidly growing literature on *x*-ray therapy elicits the importance of establishing the lethal *x*-ray dose for malignant growths and the various efforts at standardization that have been made mostly by physical methods employing ionization chambers and the crystal spectroscope. Although a biological calibration has been attempted, little attention has been paid to the histological phase, the reactions of the cells. The first systematic effort along this line was made by Becton and Colwell in 1911, but since the development of *x*-ray apparatus of much higher voltage, their work seems inapplicable to-day.

It has long been known that the mitochondrial content varies with the metabolic activity of the cells, decreasing progressively during the last stages of cytomorphosis and increasing at the height of activity. The abundance of mitochondria in embryonic tissue, the relative increase in thyroid cells during hyperthyroidism, and the complete absence during senility of cells (Cowdry, Lewis and Lewis, Duesberg, Goetsch) are examples of such alterations. The neutral red bodies or degeneration vacuoles (Lewis, 1919), on the other hand, tend to increase in the dying cell as long as it remains viable.

Our work of which this is a cursory report employs the cytoplasmic inclusions, the mitochondria and neutral red bodies as criteria of cell reaction and cell injury after *x*-ray with the hope of throwing some light on the lethal tumor dose.

The examination of fresh tissue, when supplemented by an examination of fixed material and transplantation into the living animal, constitutes the method of choice for the study of mitochondria specifically stained by Janus green, and of the degenera-

tion vacuoles stained by neutral red. Such a method has the advantage of studying tissue which is alive, or that which has undergone little alteration after removal from the host. Besides the technique is simple and rapid (Prigolen, 1921). Our procedure in these experiments briefly stated is as follows: A group of six animals is subjected to the x-rays for varying periods of time. Each animal as well as the control is anesthetized, a wedge of tumor tissue excised, a piece of which is dropped into warm Locke solution; another fixed and the remainder inoculated into twelve animals. On the successive days as long as the animals survive bits of tissue are removed and examined.

A careful histological study by this method of normal unrayed tumors designated numbers 180, R10, R9, R8, JRS, FRC, etc., at the Crocker Institute of Cancer Research revealed the facts that mitochondria are demonstrable by Janus green, but are less responsive than those of lymphocytes; they resist penetration of the dye, the maximum coloration appearing one hour after the application of the dye solution. Since most of these tumors undergo necrosis very readily neutral red bodies are found in small and varying numbers in the dying cells; the number depending upon the integrity of the tumor at the time of examination. Only occasionally are tumor cells impermeable to the stains.

In number, morphology, and cytoplasmic distribution, the mitochondria of tumor cells resemble those of embryonic tissue. The morphology of mitochondria varies, the granular forms predominate in most of the tumors, grouped to form bead-like chains. Definite rods are manifest only in the spindle cells of tumor R10, a polymorphous sarcoma. A delicate pleomorphic form resembling a Pfeiffer bacillus is frequently encountered in the cells of tumor No. 180. The mitochondria are uniformly distributed throughout the cytoplasm; no definite polarity being observed. Occasionally there is a heaping up of the mitochondria at one point close to the nucleus suggesting an intimate relationship with the Golgi apparatus which is believed to be associated with the secretory function of benign cells. Tello, who employed

the uranium nitrate method for the demonstration of the Golgi apparatus and incidentally of the mitochondria, found that in carcinomata depolarization does occur as the tissue becomes malignant.

The study of mitochondria and neutral red bodies in tumor cells after x-ray is now under way and although only a limited number of groups of tumors, No. 180, R10, R9, R8, R39, JRS, IRS, etc., have been exposed to graduated sublethal doses of filtered rays, it appears that a definite diminution in the number of mitochondria within the cell and the number of cells showing mitochondria does take place. This diminution is most noticeable forty-eight hours after exposure.

Material extirpated immediately and twenty-four hours after raying shows relatively little change in the cytoplasmic inclusions but occasionally an edema or cloudy swelling of the cells is observed. The cells appear large and swollen, the nucleus becomes invisible and the cytoplasm has a homogeneous ground glass appearance.

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Discussion:

DR. EWING: I have been very much interested in this effort to establish a lethal sign in rayed tumor cells. It is a question that comes up constantly to one who is studying material of this sort, and one to which we would very heartily welcome an answer. I myself am often unable to give an opinion on the material which I see whether the cell has received a lethal dose or not. It is very difficult to say on morphological data whether a given cell as seen under the microscope is dying or destined to die. I would like to ask Dr. Wood whether the mitochondria demonstrated in these slides are identical with the ordinary mitochondria of normal cells, or whether it is possible that changes brought about by raying may cause an extensive transformation of the original cytoplasm, and a reappearance of granules in new forms, some of

which might give reactions attributed to the mitochondria. Do you regard these bodies as exactly the same as those which Beeton described? I believe he abandoned his claims after a longer experience. The subject seems to me however very interesting and suggestive, and I might say that from my point of view it would make very little difference whether Dr. Wood has found the right clue or not. Probably somewhere in this field of morphology a clue will be found. This method appeals to me rather more than the original suggestion of Dr. Wood that we submit our tissues to the biological test. That I think is very difficult, whereas if we could point out some specific morphological change which occurs early in the course of necrobiosis of radiated cells it would be extremely valuable.

DR. PRIGOLEN: There is nothing to add to the discussion, except that I think that the neutral red bodies may possibly prove more useful as indicators of cell injury than the mitochondria. Such degeneration vacuoles may afford better evidence than the mitochondria, but we are not prepared to make a definite statement at the present time.

DR. WOOD: I have been disappointed that the mitochondrial changes did not prove as useful as had been hoped. However, one must be accustomed to disappointments in tumor research, and so I am rather acclimated to negative results. Of course the study of fresh tissues is the phase which is important, as fixation methods take a long time. My hopes are still that within seventy-two hours after raying we will get some type of degeneration or change in cell morphology which will give us a hint which is sufficiently constant to be used as an indicator of approaching cell death.

Dr. Ewing referred to the methods of cell morphology as appealing to him more than the biological tests. By that I presume he means the implantation of tumors after raying. That method of course requires a very long time of waiting, but after all it is the fundamental and only final method, and nothing else will replace it. We have to watch our animals three months to be sure a tumor will not appear after an inoculation has taken place, because the cells are very seriously damaged, and do not grow immediately. The method, even though time-consuming, is the only test of the fact that the cell is dead or alive. Those interested in the treatment of human tumors do not seem to realize that the same method is used in man. If the human tumor grows after radiation, it is not dead; if it does not grow within a period of five or six years, one may properly assume that radiation has killed it. The only difference is that tumors in mice grow so much more rapidly that we can learn whether they have been killed or not in a few months. I hope that next year we can report that we have something of value, either mitochondria, or the neutral red bodies, or some of the other minute cytological structures which our new histology has brought out. So far we have done a large amount of work with very little result.

MULTIPLE HOMOLOGOUS TUMOR TRANSPLANTATIONS AND THEIR BEARING ON THE GENETIC PROBLEMS OF SUSCEPTIBILITY AND IMMUNITY. A PRELIMINARY REPORT

FRANCIS CARTER WOOD, M.D., AND M. R. CURTIS, PH.D.

(From Columbia University, Institute of Cancer Research, F. C. Wood, Director)

That the genetic constitution of animals is an important factor in determining the success of inoculations of grafts from a transplantable tumor should logically have been predicted from the long known facts that a tumor rarely grows when transplanted into animals of species other than the host and that races and strains of the same species respond differently to tumor inoculation. Later contributions based on transplantation into pedigreed stock are important. However the assumption made by some biologists that the genetic susceptibility of the host is the only factor concerned in the fate of a tumor graft is quite as narrow a point of view as to disregard such susceptibility altogether.

That the genetic constitution of the animal is often not the deciding factor in determining either the inoculation outcome or the rate of growth of resulting tumors has been shown by a series of experiments at the Crocker Institute of Cancer Research. In these experiments each of several hundred mice were inoculated simultaneously in four different sites (both axillæ and both groins) with grafts from Crocker Fund mouse sarcoma No. 180. Now it is fairly obvious that the genetic constitution of these four sites in any particular animal is the same, yet the inoculation did not result either in four tumors of equal size or no tumor as would be expected if the genetic factor was the all important one. Of the 413 animals which lived for two weeks after inoculation only one failed to produce any tumor; 5 produced only one tumor; 20 produced two tumors; 95 produced three tumors and 292 produced four tumors. Only the one

animal which failed to respond to all four inoculations could be considered immune, yet of the 1,652 grafts, 154 failed to grow, that is, although only 1 of 413 animals, or 0.24 per cent., was immune, 9.32 per cent. of the inoculations were unsuccessful.

The 413 animals were in five series. The material for the inoculation of each series was selected from a single tumor and care was taken to insure the distribution of the grafts so that two sites in the same animal were no more likely than any other two sites in the series to receive grafts which were contiguous areas of this tumor. Each series showed successful and unsuccessful inoculations, the respective proportions of which may be represented by p and q . If the individuality of the animal had nothing to do with the fate of the graft so that a graft was as like to grow in one animal as in any other we would expect the successful and unsuccessful inoculations to be distributed into n groups of 4 (n being the number of animals in the series) according to the laws of chance. That is, the most probable expectation of 4, 3, 2, 1 and 0 tumors would be represented respectively by the five terms of the binomial $n(p + q)^4$. For each of the five series this theoretical distribution was calculated and compared with the observed distribution by Pearsons'¹ method for testing goodness of fit and the probability in 100 trials of a fit as bad or worse than the one observed was determined. These probabilities for the five series were respectively 96.5, 78.0, 64.9, .4, and .0009. That is in three of the five series the theory of a chance distribution of the successful and unsuccessful inoculations fits the observed facts very well. By combining the theoretical distributions for the five series we have as the sum of the most probable expectations² of 4, 3, 2, 1 and 0 tumors 287.4, 101.0,

¹ Tables for Statisticians and Biometricians, London, 1914.

² If we calculate the most probable expectation of 4, 3, 2, 1 and 0 tumors on the basis of an even distribution of takes and non-takes throughout all the experiments, that is, with $p = \frac{1498}{1652} = .90678$ and $q = \frac{154}{1652} = .09322$, we would have as our most probable expectation in 413 animals the five terms of the binomial $413 (.90678 + .09322)^4$ or 279.23, 114.82, 17.71, 1.21 and .03. This distribution differs significantly from the one observed but since the five series differ from one another in the percentage of successful inoculations the grouping together of the data is not warranted. That is, the difference between

21.0, 3.3, and .3. Figure 1 shows the graphic comparison of this sum of the theoretical distributions with the sum of the observed distributions or 292, 95, 20, 5 and 1.

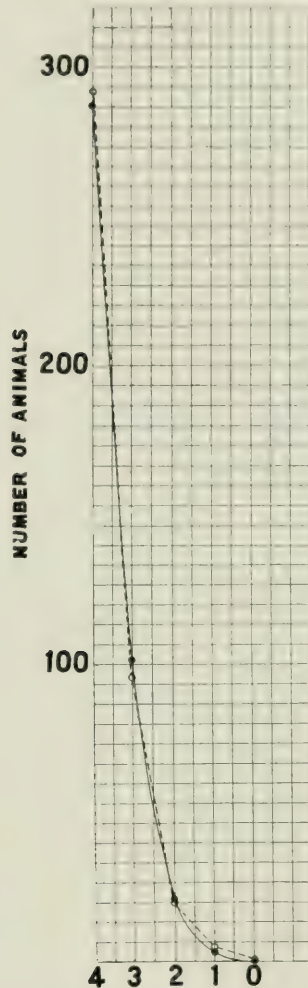


FIG. 1. Broken line = observed frequency in the five series combined. Solid line = sum for the five series of the frequencies expected if chance determined the grouping of positive and negative inoculations.

That this more nearly describes the observations than the theory of four tumors or no tumor is obvious.

Further the two, three, and four tumors in the same individual leads to a spurious probability of the grouping of successful or unsuccessful inoculations in any animal selected at random. Nevertheless this distribution more nearly fits the one observed than the grouping of four tumors or no tumor expected if the susceptibility or immunity of the animal decided the fate of the graft.

vidual were not of equal size when the experiments were concluded and the animals killed two weeks after inoculation. In four of the five series the tumors were removed and weighed, while in the fifth series the mean diameter was used as a measure of size. A statistical study was made of these data. For each series the correlation coefficients were calculated between the size (measured by weight in the four series and by mean diameter in the fifth series) of

1. Right axillary and left axillary tumors.
2. Right axillary and right groin tumors.
3. Right axillary and left groin tumors.
4. Left axillary and right groin tumors.
5. Left axillary and left groin tumors.
6. Right groin and left groin tumors.

These coefficients or their ratio to their probable errors tell us whether or not the tumors in two different sites in one animal were more nearly the same size than tumors from the same sites in other animals in the series. There were thirty of these coefficients, *i.e.*, six for each of the five series. Sixteen of these were positive and more than three times their probable error and therefore probably significant. Six were positive and between two and three times their probable error. Seven were positive and less than twice their probable error, while one was negative. The absolute values of the significant coefficients were a long way from $+1$, the coefficient of perfect correlation theoretically expected if all the tumors in each individual were the same size. The five highest coefficients were $.521 \pm .051$, $.498 \pm .053$, $.443 \pm .063$, $.430 \pm .076$ and $.427 \pm .095$. These results indicate that the tumors in the same individual were in general more nearly equal in size than would be expected if their association was due to chance. However, other factors reversed this relationship between the tumors from two sites in a particular series.³

The results of this set of experiments force us to the conclusion that there are probably many factors which determine

³ In series 180/86 G' the correlation coefficient between the weights of left axillary and left groin tumors was $-.281 \pm .117$.

the fate of a tumor graft and that the physiological or anatomical peculiarities of the host which include but are not necessarily confined to its genetic constitution are not necessarily the deciding ones.

THE SALT METABOLISM OF TUMORS

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The present paper is a preliminary report; the full paper appeared in the *Journal of Cancer Research*, 1922, vii, 417.

In an attempt to further elucidate the peculiar behavior of tumor-bearing rats with reference to the carbohydrate metabolism after the injection of protein,¹ microchemical examinations of various types of benign and malignant tissues were made. Among the various chemical substances sought for in both benign and malignant cells were the various salts, which were stained according to the methods described by Macollum. In confirmation of the work of others, irrespective as to the type of cell, *i.e.*, benign or malignant, actively proliferating or quiescent, the potash was found to be present in the cell cytoplasm and pericellular fluids, the calcium in the nucleus, cytoplasm and pericellular fluids, and the soda in the pericellular fluids. The phosphates were found in the cytoplasm and nucleus, and occasionally in the pericellular fluids, while the chlorides and sulphates were found only in the pericellular fluids and the cell wall.

Estimation of the salt deposit in the microscopic preparations indicated that receding tumors contained less potash and more calcium than did growing tumors, apparently confirming results obtained by Beebe and Buxton, and Clowes and Frisbie. In addition it was noted that there were more cells per given area in a receding than in a similar area of growing tumor.

Estimations of the potash, soda, and calcium content of the blood of animals bearing transplanted progressively growing

¹ For a report of these experiments, see *Jour. Cancer Research*, 1921, vi, 223.

tumors, and of the same tumor strain undergoing spontaneous recession, as well as of the blood of animals bearing spontaneous liver tumors, were made after the method described by Kramer and Tisdall. In a similar manner the salt content of the tumors themselves and of other tissues of the body not involved in the tumor process was also determined.

It was found that the parenteral introduction of living homologous cells, irrespective as to whether these cells were malignant or benign, caused a demineralization of the blood, and that the same condition occurred when malignant cells arose in the host *de novo*. When the cells which had been introduced died, *i.e.*, the tumor spontaneously receded, there occurred a hypermineralization of the blood which in turn disappeared when the dead cells were completely absorbed. This occurred irrespective as to whether the cells that were dead were benign or malignant.

While these changes were going on in the blood an analogous series of changes was occurring in the testes. As the transplanted tumor grew the testes became demineralized, and as the tumor receded, the organ became hypermineralized, to return to the normal when the tumor had been completely absorbed. The transplanted tumors themselves showed marked demineralization during the process of recession. When the tumors were spontaneous in origin the organ in which the growth arose showed a hypermineralization more marked than that which took place in the tumor itself.

With these changes in the total salt content there also occurred a change in the ratio of the various salts. When living cells (irrespective as to whether they are benign or malignant) were parenterally introduced, both the potash and soda ratio, as compared with the calcium in the blood stream, were reduced. When these cells died, the potash partially returned to the normal ratio, while the soda exceeded the normal ratio by as much as 100 per cent. The ratio in the blood of spontaneous tumor-bearers is analogous to that found in those bearing spontaneously receding transplanted tumors, a fact probably explainable by the large amounts of dead tissue present in spontaneous tumors.

When the ratio of potash to soda is taken, there is evident a marked increase in the soda in the blood of those bearing receding transplanted or spontaneous tumors.

In the tissues not involved in the neoplastic process a similar series of changes is observed. The introduction of living cells caused in the testes a reduction of both potash and soda when compared with the calcium, while when the introduced cells died and were absorbed there was a partial return to the normal. In the liver in which a spontaneous tumor has developed, there was a reversal of the normal, for while in the normal there is twice as much soda as potash, in the spontaneous tumor liver the potash and soda were about equal. In both spontaneous and transplanted growing tumors the potash and soda were about equal in ratio when compared with calcium, while in the receding tumors the soda ratio was very markedly increased.

From the results of the experiments it appears that the introduction of homologous living cells, whether benign or malignant, causes a demineralization of the blood and body tissues with a storing up of these elements in the growing cells. When the inoculated cells die the stored up mineral is again delivered to the blood and returned to the tissues. When the new cells develop in the host, *de novo*, the same demineralization of the blood occurs with a storage of the salts, not alone in the developing tumor, but also in the organ in which the tumor arises. With these changes there occurs a disturbance of the ratio of the salts in their relation one to the other, most of the increase being in soda, and the decrease in potash.

Other experiments which will not be detailed here indicate that these changes are secondary to the growth and death of the cells and have no relation to either the genesis or spontaneous recession of the tumors.

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CEREBRAL CYST IN AN INFANT

H. G. JACOBI, M.D.

(From the Pathological Laboratory, Lenox Hill Hospital, New York)

Cysts of the brain are not only of infrequent occurrence, but their detection clinically is extremely difficult and in the majority of cases the condition is diagnosed only at post-mortem examination. In reviewing the literature upon this subject, it is interesting to note that Starr, collecting 299 cases of brain tumors in children, showed that 30 of these, or nearly 10 per cent., were cysts. Their locations were as follows: basal ganglia and lateral ventricle 1, pons 1, medulla 1, base 1, multiple 2, cerebellar 9, centrum ovale 15. Several interesting cases have been reported occurring in adults. Anglade reported a case of hydatid cyst of the brain in a female forty-four years old, afflicted with epileptiform seizures and hemiparesis of the left side, dulling of the intellect, dysarthria, and an intention tremor. The cyst was located beneath the posterior horn of the lateral ventricle of the left side and measured about 6 cm. in long axis and 4 cm. in width.

Ross reported a case in a female, fifty-five years old. This patient had mental symptoms, hemiparesis on the left side, cerebellar ataxia, and an intention tremor. Here the cyst was situated in the anterior part of the third ventricle, arising as a simple retention cyst from the connective tissue of the velum interpositum. Lambert, Hoppe, Hunt, and Remsen have reported similar cases.

Our patient showed several interesting features which briefly were as follows: (1) The sudden onset of symptoms simulating an acute infectious process. (2) Indefinite signs and symptoms, making an antemortem diagnosis impossible. (3) The presence of a hyperglycemia and glycosuria.

The patient, a male infant one year of age, was admitted on October 28, 1922, with the complaint of vomiting and drowsiness of one day duration. The past history was negative except that three weeks prior to admission the patient had several attacks of vomiting, extending over a period of two days. These occurred without any regularity or relation to the intake of food, and ceased on the next day. The family history revealed that the first child had died at an early age from an unknown cause. The second child was living and well and the father was definitely tuberculous.

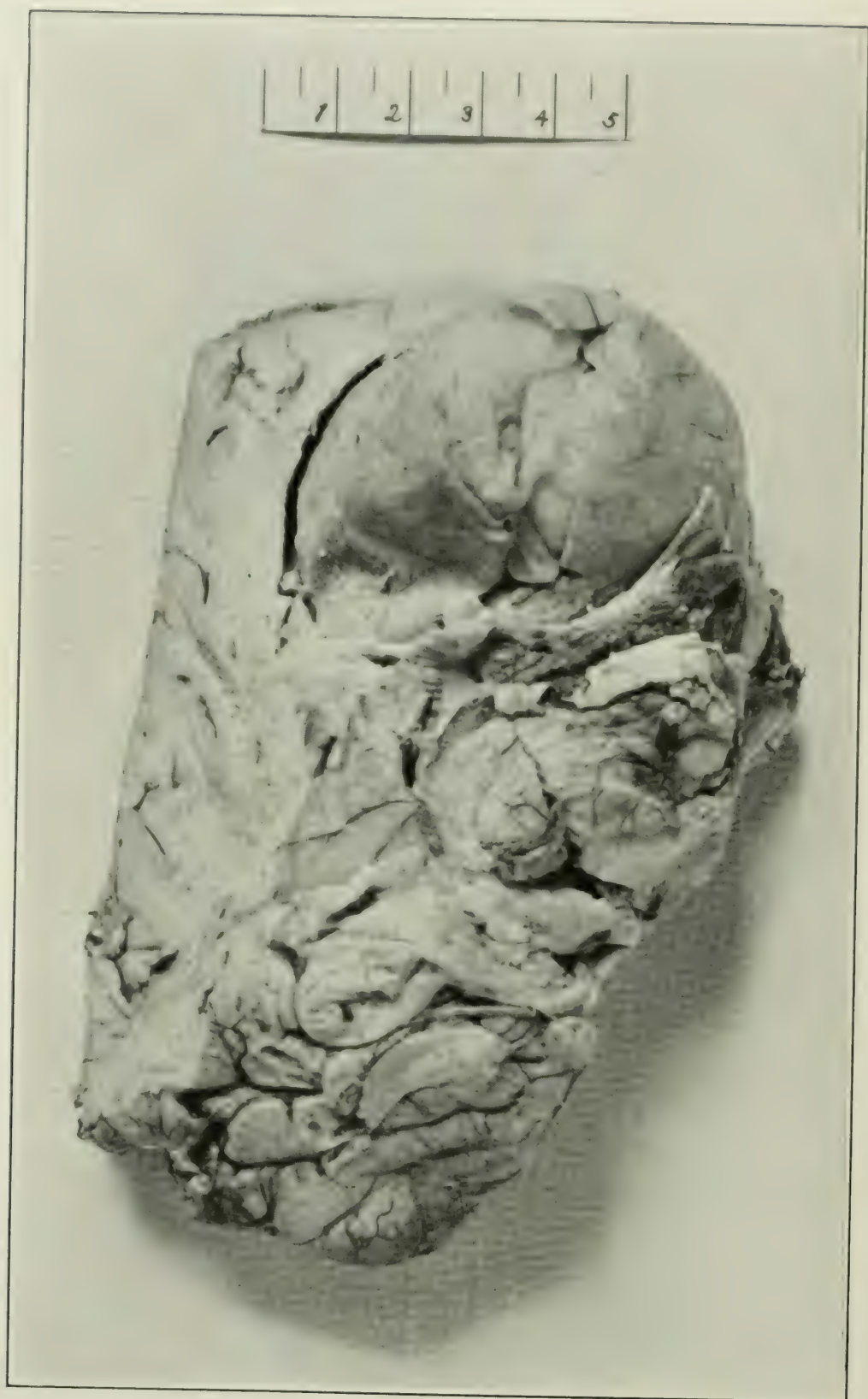
The present history was that the child had vomited twice on the morning previous to admission, had appeared drowsy and out of sorts. On the day of admission he was semi-comatose. The infant was extremely restless and its sleep had been interrupted by sharp sudden outcries. Occasionally convulsive movements were noticed, during which the head would be thrown back, the abdomen arched forward, and the extremities extended.

When examined on admission the infant was found in a comatose state, breathing rather heavily. The entire body was completely relaxed and felt cold. The pulse was 82 per minute and irregular, both in rate and in force. The temperature was 95.6° Fahrenheit, the respirations 40. There was a bilateral ptosis present and both pupils were dilated and failed to respond to light reflex. The corneal reflex however was still present and the eye-grounds, ears, and nose were negative. The tongue was coated and protruded from between the lips, which were dry. The other positive findings were signs of beginning pulmonary edema; weak and irregular heart sounds; distended bladder; exaggerated knee-jerks; the presence of a Babinski reflex but no ankle clonus or Kernig reaction.

The laboratory findings were as follows:

White blood cells, 25,000. Polymorphonuclear leucocytes, 82 per cent. Lymphocytes, 18 per cent.

Lumbar puncture showed the spinal fluid to be under normal pressure, clear, and having a cell count of 900, of which 78 per cent. were lymphocytes and 22 per cent. polynuclear leucocytes. Culture of the fluid was sterile and the globulin reaction was markedly positive.



Section of right cerebral hemisphere showing cyst, posteriorly situated with lateral ventricle removed

Chemical analysis of the blood showed a creatinine content of 0.7 mg. per 100 c.c. of blood, and a sugar content of 175 mg.

Urine examination on admission showed specific gravity of 1.011, straw color, no albumin, and the presence of a considerable amount of reducing substance. The following day a second examination revealed a positive albumin and 0.8 per cent. sugar. The sediment contained a few epithelial cells and many bacteria.

The patient continued in a comatose state with the temperature gradually rising until it reached 105° the following evening. The pulse became more rapid. The edema of the lungs became more marked and death occurred from respiratory failure about thirty hours after admission.

The positive findings in the post-mortem examination were as follows:

Upon opening the calvarium an excessive amount of cerebro-spinal fluid escaped. The convolutions of the brain were markedly flattened, more so over the right than the left hemisphere. There was a marked edema involving the pia of the brain. Upon opening the lateral ventricles, the left was found to be considerably distended, as was the right. Beneath the posterior horn of the lateral ventricle of the right side and separated from the ventricle by 0.2 mm. of brain tissue was a fluctuating cyst on the surface of which were numerous newly formed blood vessels of fair diameter. The cyst distorted the lenticular nucleus and was not adherent to the brain tissue, from which it could be shelled out. The outer surface of the brain in the posterior convolutions covered the cyst to a thickness of 0.3 cm. The cyst wall was thin, dense, and white in color. It contained 60 c.c. of a creamy yellowish fluid, the chemical analysis of which will be given later. Its cellular content consisted of a large number of lympho-cells undergoing fatty degeneration.

Both lungs showed in their posterior and inferior aspects a diffuse edema without areas of consolidation.

The liver, pancreas, gall bladder, adrenals, bladder, ureters, kidneys, gastrointestinal tract, and spleen were normal. The lymph glands of the mesentery of both large and small gut were enlarged, measuring 0.04 to 1.2 cm. in diameter, and were pink in color. There was a secondary paralytic ileus involving the last half of the small and the first half of the large intestine.

Microscopical examination: The mesenteric glands showed a partially healed tuberculous process.

The cyst wall was composed of a dense laminated connective tissue richly infiltrated with round cells and having adherent to its inner surface a fair number of polymorphonuclear leucocytes.

The contents of the cyst consisted of a cloudy greenish fluid, colloid in nature, the chemical examination of which revealed the following. It proved to be insoluble in water and acetic acid, but was dissolved by dilute potassium hydroxide. The principal constituent was pseudomucin, which yielded a carbohydrate (glucosamine). Its specific gravity was 1.029. The total nitrogen was 1.3 gm.; total protein (Purdy method), 2.78 gm.; uric acid, 5.5 mg. per 100 c.c.; creatinine, 0.085 mg.; potassium, 0.04 mg.; calcium, 0.0116 mg.; sodium, 0.162 mg.; chlorides, as NaCl 0.360 per cent., and cholesterol 200 mg. per 100 c.c. This type of cyst according to Hammersten may be considered to be of the proliferative type, the characteristic constituents of which are metalbumin and paralbumin.

The presence of a hyperglycemia and glycosuria in this case is of interest. It is rather difficult to say whether their presence may be regarded as part of a terminal condition or whether pressure of the cyst upon the fourth ventricle stimulated the so-called carbohydrate centre simulating the puncture diabetes of Claude Bernard.

The formation of cysts in the brain has been attributed to a variety of causes. Bruns, while admitting that the etiology of such cysts remains largely in doubt, offers the following classification: (1) Those of congenital origin. (2) Parasitic. (3) Traumatic. (4) Those resulting from brain softening. (5) Those without any accountable etiology. Various other classifications have been made, none of which seem to cover the field completely.

With regard to those of congenital origin, we note that Bruns has reported that in several cases of glioma of the pons he has also found minute cysts lined by ependyma. These were considered as separations from the primary neural tube. Stroebe in connection with gliomata of the brain likewise found small cysts lined by columnar epithelium. Thus abnormalities in the primary neural tube anywhere along its course may be the focus of a morbid proliferation. The dermoid cysts may be similarly regarded as of congenital origin. These are exceedingly rare and Cushing reports but one case in his very large experience. Another variety of congenital cyst was described by Heschl and Kundart. This is the so-called porencephalic cyst, where a defect exists in the cortex extending down to the ventricle. This occurs usually in the region supplied by the middle cerebral artery.

Cysts of parasitic origin are due either to the cysticercus or more rarely to the echinococcus. Hunt states that they may be pathologically differentiated from the congenital group in the following manner. (1) In the congenital type the cyst wall throughout is made up of medullated nerve fibres and glia. (2) The cyst is not intercalated but forms an integral part of the stem. (3) There are remnants of epithelial lining present.

Traumatic cysts around penetrating spicules of bone are at

times encountered and may give rise to considerable destruction of brain tissue. Hoppe cites a case where a cyst the size of a cherry developed in the substance of the left temporo-sphenoidal lobe as a result of a depressed fracture. The fracture was overlooked because it was covered by the temporal muscle.

Various circulatory disturbances occurring in the brain may give rise secondarily to cyst formations. The blood cysts which result from cerebral or cerebellar apoplexy and those following cerebral softening after embolism may be included in this group.

Inflammatory processes involving the brain substance may be responsible at times for the presence of cysts. It is a well-known fact that the power of brain cells to regenerate is limited and so with the removal of the debris, resulting from the breaking down of the brain tissue, there develops a defect which may go on to cyst formation.

Localized encysted cerebro-spinal fluid has been frequently encountered both on the surface of the cerebellum and the cerebrum. Placzek and Krause describe the condition as resulting from inflammatory changes in the arachnoid which is thickened and may be united to the dura by adhesions. Fluid collects within the meshes of the arachnoid and is walled off by these adhesions. Such changes may also occur secondary to localized meningo-encephalitic attacks with cortical destruction, seen in children, where they usually occur in connection with the underlying pathology of infantile cerebral palsy. This group constitutes the so-called arachnoidal cysts.

We finally come to a group which result from secondary degenerative changes. These occur in the various neoplasms involving the brain, and are sometimes referred to as simple serous cysts, or as cystosarcoma, cystoglioma, etc. Fraenkel reports in great detail a series of eight cases, three cerebral and five cerebellar. Of these the three cerebral and one of the cerebellar were due to degenerative softening of gliomatous origin. In the group of four remaining cerebellar cysts, one was due to softening of a carcinomatous metastasis, one to hemorrhagic softening, one to anemic softening resulting from marked vascular disease, and one was without any associated condition.

Exactly where the case presented in this report belongs in the above classification is rather difficult to state. By a process of exclusion, we would be inclined to list it among those of congenital origin. The chemical analysis of its contents establishes its proliferative nature, while the pathological picture is obscured by secondary inflammatory changes.

POLYCYSTIC DISEASE OF THE KIDNEY

ABRAHAM TOW, M.D.

(From the Pathological Laboratory, Lenox Hill Hospital, New York)

Polycystic disease of the kidney is a condition that, although believed to be always congenital in origin, most frequently manifests itself in later life. Often the condition is unsuspected and is found only in the course of a routine post-mortem examination. A number of cases have been reported in infants and here the diagnosis is not particularly difficult if bilateral tumors dating from birth are present in the kidney region. Ritchie in a series of 88 cases, gave the age in 75. He found the age limits between 23 and 88, and 45.3 as the average age.

There has been a great deal of discussion about the etiology. Virchow believed the condition due to a papillitis *in utero* produced by the irritation of uric acid and lime infarcts. Brigidi and Severi with others have advanced the claim that it is a multilocular adenocystoma. Von Mutach in a study of cystic and embryonal kidneys, recognized the striking embryonal characteristics of the cystic kidney and believed that maldevelopment was the cause. Perhaps no one theory may be applied to all cases, but the last mentioned one is the most favored today.

Polycystic kidney seems to have an hereditary basis. Dunder cites Virchow's case of four children of the same mother in all of whom polycystic kidneys were found. He also mentions five children of the same mother; a father, son, and nephew; and a father, son, and sister with symptoms in other children in the same family. Other congenital defects have been found along with the congenital cystic kidneys, *viz.*: hare-lip, cleft pal-

ate, cardiac defects, meningocele, spina bifida, anomalies of excess, or absence of extremities, hypospadias, and atresia and absence of the bladder. Liver cysts have been found in 19 per cent. of the cases reported by Lejars, Luzatto, and Johnson. The condition is usually, but not always, bilateral. Osler, summing up the work of Ritchie and Lejars, found three unilateral polycystic kidneys in the report of 150 cases.

The following cases are of interest because they illustrate aptly many of the points mentioned above. In presenting them the unimportant details of the case reports will be omitted.

Case 1: A male infant, six weeks old, was admitted to the A. Jacobi Division for Children of the Lenox Hill Hospital, on September 16, 1922, with a negative history except for the presence of two masses, one in each lumbar region, dating from birth.

Physical examination revealed a slightly enlarged heart, a double hydrocele, and two large, nodular masses, one in each lumbar region, extending from the costal margin to the crest of the ilium. The urine, examined at intervals during the course of the disease, showed a specific gravity that was practically constant between 1.009 and 1.010 with a slight trace of albumin and an occasional granular cast and leucocyte. The phenolsulphonaphthalein determination done on admission and two weeks before death showed on the first examination an excretion of 5 per cent. of the dye in two hours and forty minutes, and 8 per cent. in two hours on the second examination. Both were without catheterization. It is interesting to note that a trace of the dye was found ninety-three hours after the first injection and eighty-four hours after the second injection. In a control done on a child aged eleven months with a normal urine, 61 per cent. was excreted in two hours, and the dye had been completely eliminated after twenty hours.

Repeated blood counts done on admission and during the course of the disease showed from 70 to 55 per cent. hemoglobin. The red cell count was 5,000,000 on admission and 4,000,000 before death. The white count varied between 6 and 8,000 cells with 70 per cent. lymphocytes and 30 per cent. polymorphonuclears. The Wassermann reaction was negative. Radiographic examination showed the heart to be enlarged. The eye grounds were negative.

Chemical examination of the blood gave the following in mg. per 100 c.c.

	Normal	Sept. 21	Sept. 28	Oct. 11
Urea Nitrogen.....	(12-15)	38.4	50	26.3
Creatinine.....	(0.5-2)	2.2	1.2	2.36
Uric Acid.....	(1-2.5)	3.7	4	2.8
Sugar, per cent.....	(.08-.12)	.084	.086	.160
Cholesterol.....	(150-200)		100	188
CO ₂ Combining Power Volumes per cent. per 100 c.c. Blood Plasma.....	(53-77)		41	

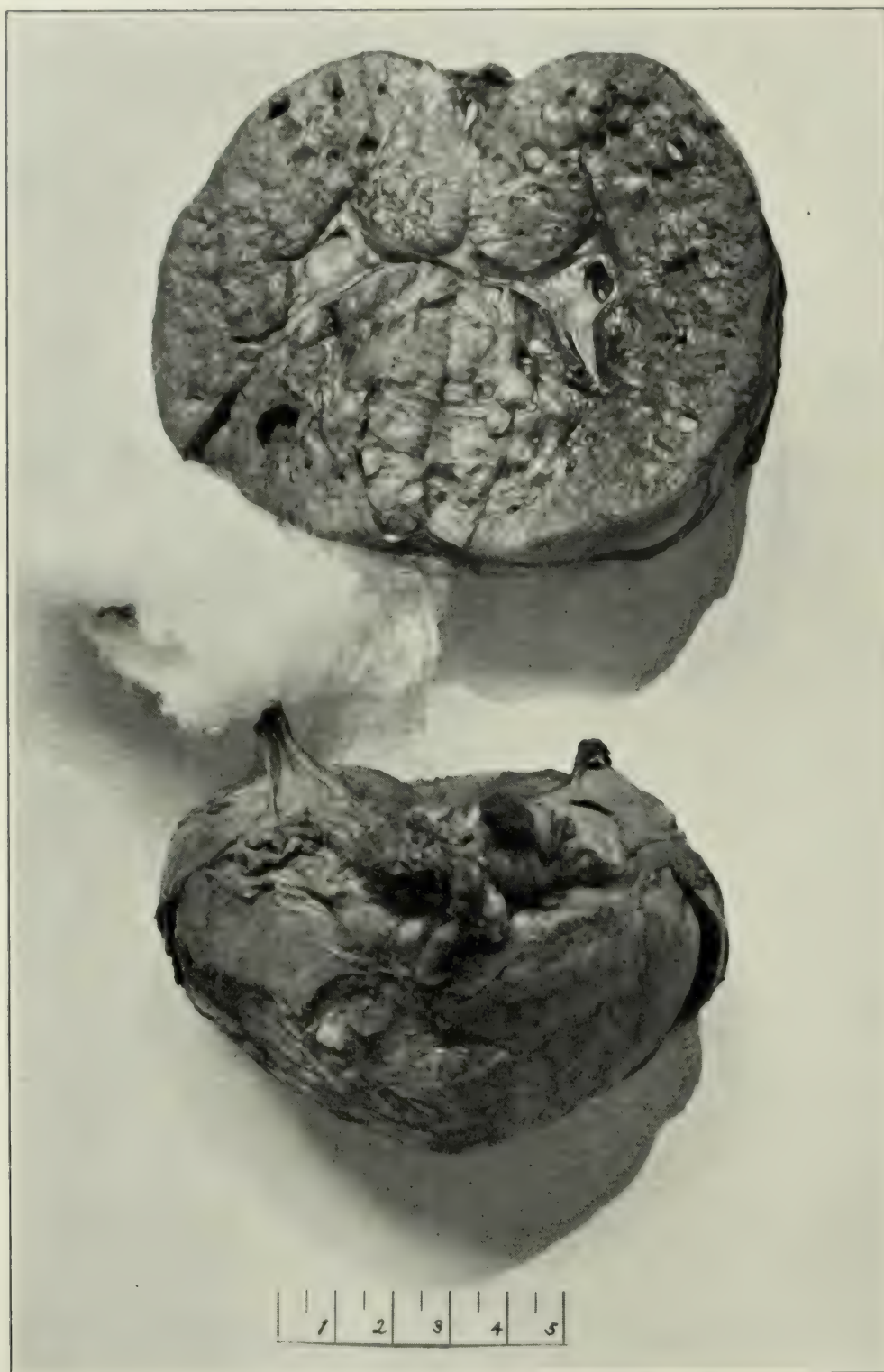


FIG. 1. Case I, polycystic disease of kidneys in infant

In summary: Examination showed a six weeks old infant with

1. Bilateral, congenital abdominal tumors.
2. An enlarged heart.
3. Signs of chronic nephritis, *viz.*:
 - (a) Albumin and casts in the urine with a low specific gravity.
 - (b) Diminished excretion.
 - (c) Nitrogen retention.

The diagnosis of polycystic disease of the kidney was made. The clinical course was uneventful until the day before death when the patient became slightly cyanosed and dyspneic for a few seconds. Death came suddenly with signs of pulmonary edema.

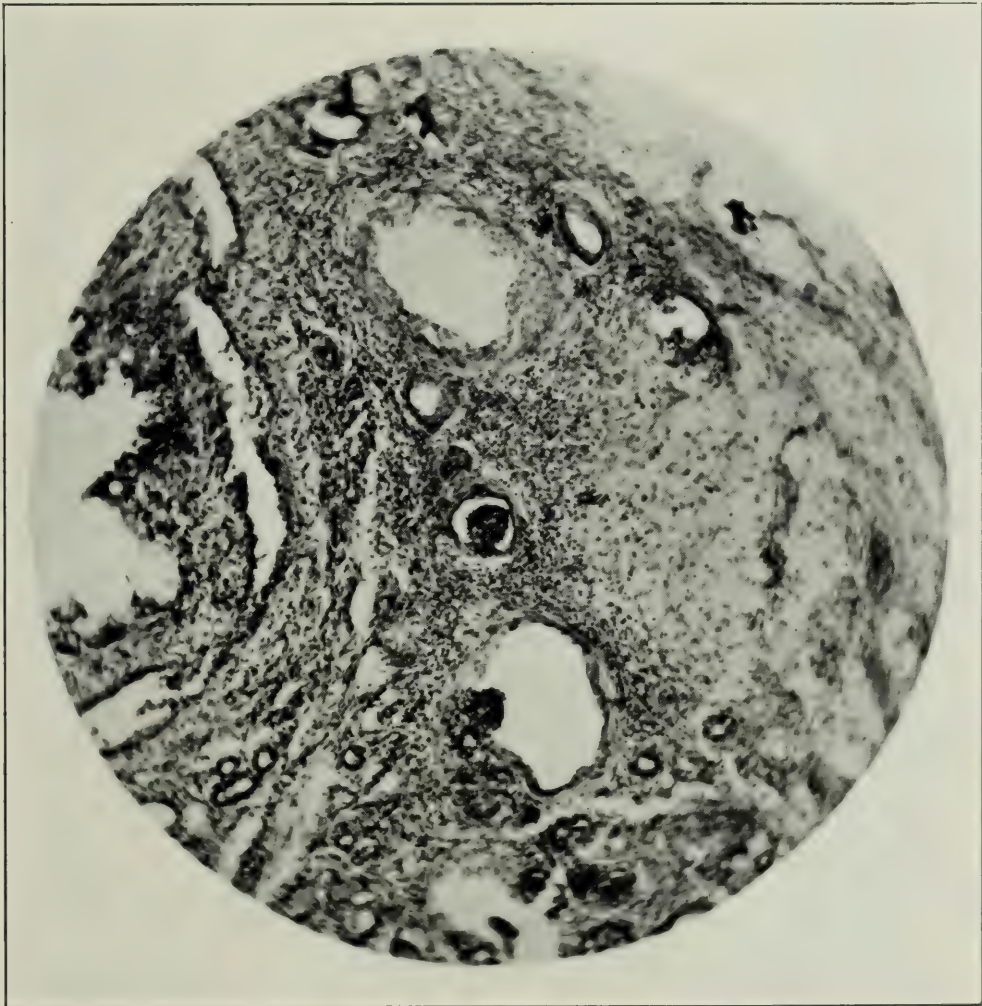


FIG. 2. Case 1, low power photomicrograph

The diagnosis was confirmed by post-mortem examination. The pathological report was as follows: The body is that of a somewhat emaciated male infant, 46 cm. in length, weighing 3.635 gm. The abdomen is protuberant and

is almost completely filled by a bilateral smooth tumor mass. Rigor mortis is present. The pupils are dilated.

Upon opening the calvarium an excessive amount of cerebro-spinal fluid escapes. The pia is very markedly edematous and the convolutions on the inferior portion of the fore-brain show marked flattening. The lateral ventricles are slightly distended.

Both pleural cavities contain approximately 50 c.c. of clear fluid. The pericardium contains about 20 c.c. of clear fluid. The thymus is persistent. Both lungs in their posterior, inferior portions are markedly edematous, but without gross evidence of consolidation. The heart weighs 35 gm. and measures $4 \times 3 \times 4$ cm. in diameter. The left ventricle has the greatest amount of hypertrophy.

The peritoneal cavity contains no fluid. The gastro-intestinal tract, adrenals, bladder, testes, ureters, gall bladder, as well as the pancreas are grossly normal. The liver is normal in size and on gross section shows no abnormalities. The spleen is slightly increased in size and on section is firm.

The right kidney weighs 190 gm. and measures 9.5×5 cm. The left kidney weighs 180 gm. and measures 9×5 cm. Both kidneys on section show innumerable cysts which vary in size from 0.1 to 0.6 cm. There are also innumerable smaller cysts which can be seen with a hand lens. No margin of kidney tissue is demonstrable.

Anatomical diagnosis: Edema of the brain; bilateral pleural effusion; edema of the lungs; cardiac hypertrophy; bilateral congenital cystic kidney.

Cause of death: Edema of the brain; edema of the lungs.

Microscopical examination of the heart and liver shows no lesion.

The lungs show a slight edema.

The spleen shows a moderate degree of congestion and fibrosis.

The kidneys show a dense hyaline stroma in which there are a few isolated areas of fairly normal kidney epithelium; the larger portion of the specimen consists of cyst-like spaces lined by from one to twelve and fourteen rows of low cuboidal epithelium.

Case 2: A female, sixty-four years old, died of pneumonia following an operation for carcinoma of the breast. The patient had a cleft palate and was very obese. Her urine was negative. In the course of a routine post-mortem examination polycystic kidneys were found. At no time had there been any suspicion of such a condition.

Case 3: A male, thirty-eight years old, was admitted to the service of Dr. Hensel with the complaint of headaches and black spots in the field of vision on and off for the past five years, and sharp pains in the left flank for the past week, with increased frequency of urination. There were no other urinary symptoms. The patient has a brother with kidney disease.

Physical examination was negative except for tenderness and the presence of a mass in the posterior upper left quadrant. This mass could not be well defined due to muscle spasm. The blood pressure was 160 systolic and 105 diastolic. The Wassermann reaction was positive. The urine was clear with a specific gravity from 1.018 to 1.020, a trace of albumin, and an occasional white blood cell, epithelial cell and granular cast in the microscopic picture.

The phenolsulphonephthalein test done on September 30 showed an excretion of 54 per cent. in two hours; 30 per cent. of the dye in the first hour, and 24 per cent. in the second hour. An *x*-ray taken after pneumoperitoneum showed both kidneys to be enlarged.

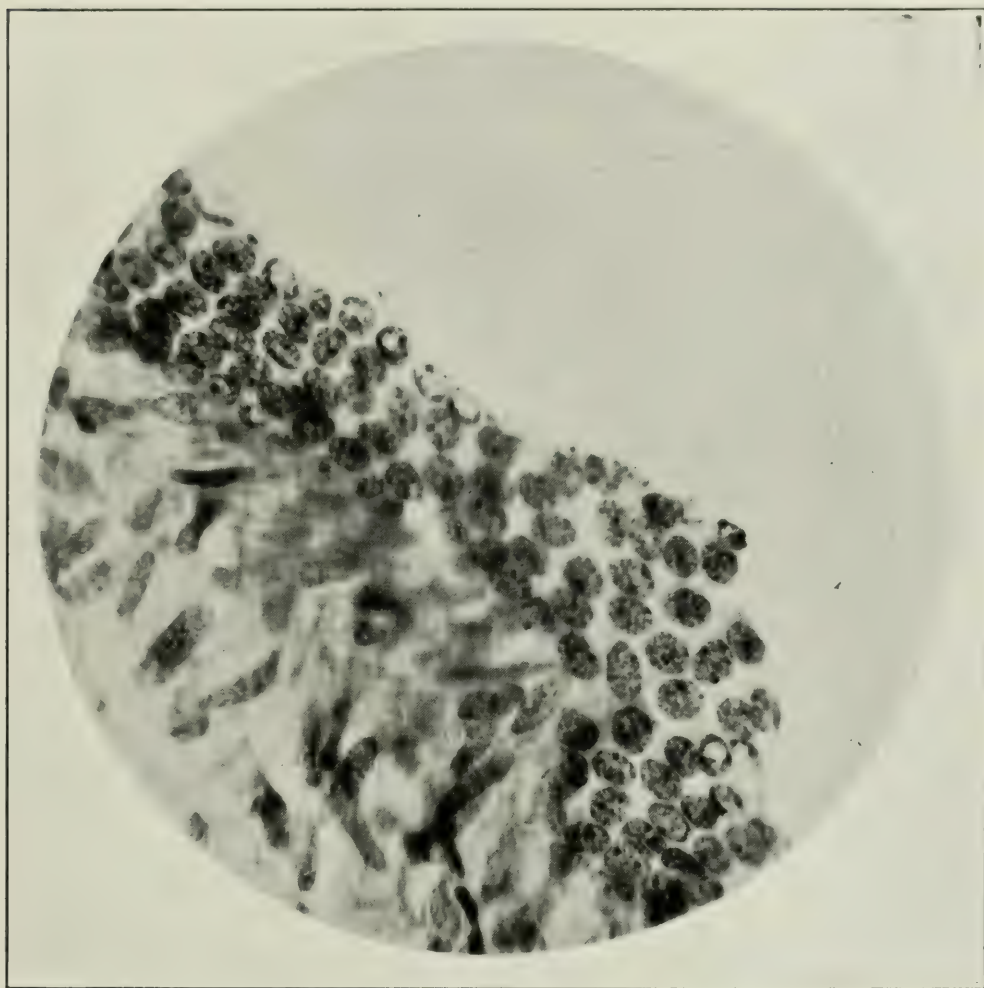


FIG. 3. Case 1, high power photomicrograph showing cells lining wall of a cyst

Examination of the eye-grounds was negative. There was some slight astigmatism present. *X*-ray of the frontal sinuses showed a slight haziness, but was considered negative. The conclusion arrived at was that the headaches were luetic or neurotic in origin and that the kidney condition did not play a part in their causation.

Chemical examinations of the blood done at varying intervals during the stay in the hospital gave the following results:

Mg per 100 c.c.	Sept 18		Sept. 26		Nov. 18	Nov. 27		Dec. 12
Urea Nitrogen	41.6	Sept. 22-25 Mosenthal Diet	15.6	Oct. 16—Laparotomy	25	22.5	Nov. 29—Dis- charge Low Protein Diet Instituted	18.5
Creatinine	3.4		2.2		1.2	1.1		1.1
Uric Acid	4.0		4.0		3.7	3.6		3.0
Sugar, per cent	.135		.116		.132	.126		.122
Cholesterol			75					

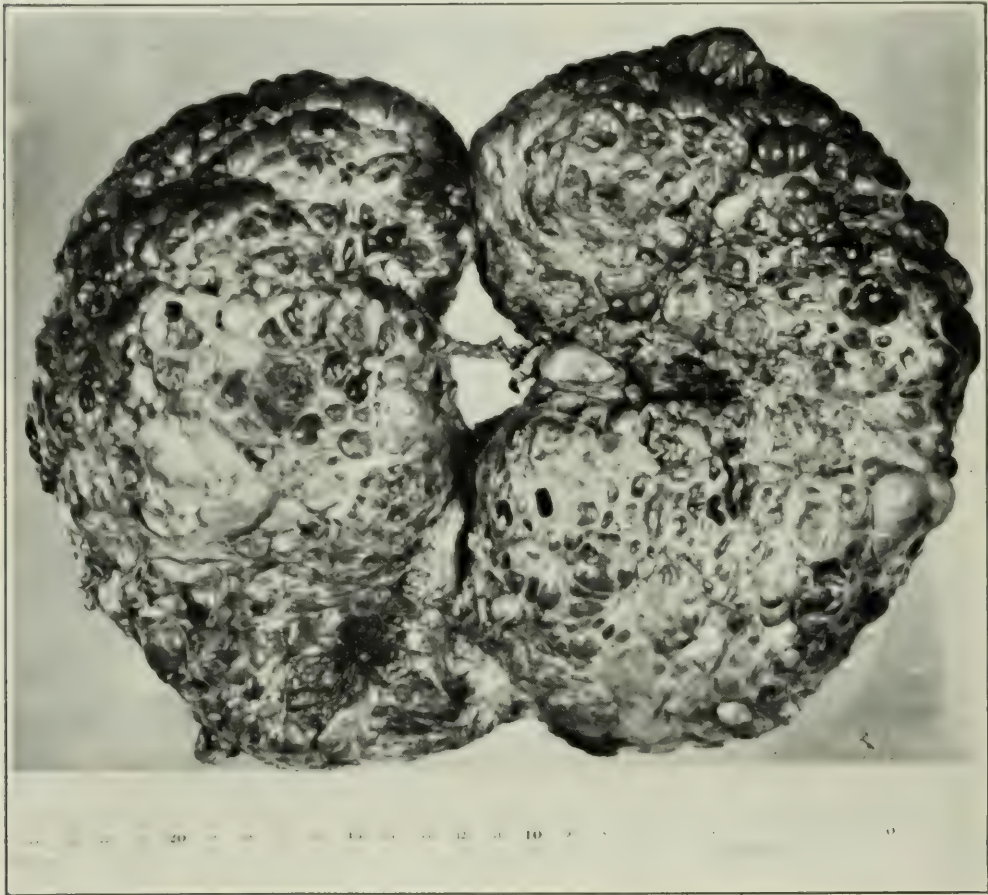


FIG. 4. Case 2, polycystic disease of the kidneys in a woman, age 64

The Mosenthal test for renal function was performed. There was no water, chloride, or nitrogen retention. The specific gravity, however, was constant, varying between 1.016 and 1.019.

Although polycystic kidney was considered as a possibility in the differential diagnosis, it was decided that the patient was entitled to an exploratory laparotomy in case the enlargement on the right side should be compensatory

to the pathological condition on the left. Examination showed polycystic kidneys of large size. Both were irregular in shape and contained a number of large cysts, especially at the lower poles, with smaller ones scattered over the rest of the surface. Nothing further was done as the surgeon did not believe that puncture of the cysts as advised by Rovsing was of value.

In a comparative study of the kidneys in cases of polycystic disease of the kidneys in infants as reported by Leopold and Kunstler, Royster, and myself and those reported in adults one is struck by the fact that in the adult kidney every case reviewed reported cysts of varying number and size on the surface. In Leopold and Kunstler's case many small cysts were also found upon the kidney surface; and Royster reports a few cyst-like elevations. But in Case 1 the cystic character of the kidneys was discovered only on section.

A study of the chemical analyses of the blood fails to show any marked nitrogen retention. Perhaps if in Case 1 the blood had been studied immediately before death, it might have shown a marked increase in the nitrogenous constituents. But here death was probably due to cardiac embarrassment. One can fully appreciate the extra work thrown upon the heart when one sees the amount of connective tissue in these tremendously enlarged kidneys. The combined weight of the two kidneys was 370 gm. In a normal infant two months old the weight of both kidneys is 30 gm.

In adults death is more often due to failure of the kidneys to function properly. Signs of uremia, especially in young adults, with a mass or fulness in one or both flanks should make one strongly suspicious of polycystic kidney. It is interesting to note that in Case 3 the lowest figures obtained at any time in the analyses of the blood were those following a three-day period on a diet given in carrying out a Mosenthal test for renal function. There was also a reduction in the nitrogen retention following the institution of a low protein diet.

Discussion:

DR. MOSHCOWITZ: In the preface to his cases Dr. Tow mentioned the three theories that have been passed down from generation to generation in regard to the pathogenesis of polycystic disease of the kidney. The theory

of Virchow of a papillitis has been well exploded, and I do not think we need to discuss it seriously. There is very little evidence that the cystic kidney is a new growth. There is to my mind no question that it is a congenital malformation, and all the evidence points that way. I think in 1906 I gave very conclusive proof that that was so, and I came to that conclusion in a study of cystic disease of the liver. There is one very remarkable thing about cystic disease of the liver. In studying five or six cases of this condition, which I had collected from all over the country, I found one remarkable phenomenon in all of them, namely, aberrant bile ducts within the lobules of the liver; in other words, these newly formed bile ducts were not limited to the capsule of Glisson, but were in the lobules of the liver itself. That seemed to point to a congenital anomaly. I thought the only way to prove that was to find, if possible, a fetus in which there were cystic kidneys and in which the liver appeared normal grossly. In addition, it was important to find, if possible, some congenital malformation. By a strange coincidence there was a fetus that had six fingers and six toes and spina bifida in the Pathological Laboratory of the College of Physicians and Surgeons which I studied through the kindness of Dr. Larkin. It also had bilateral disease of the kidney, but the liver looked normal grossly. On section, however, this liver showed these intralobular aberrant bile ducts that I had seen in cases of cystic liver as found in adults. This seemed to prove that the condition was a congenital malformation. Embryologically, it is perfectly consistent. These livers are simply primitive forms of livers which have not fully developed from the primitive bud from the enteroderm, and, as a matter of fact, that type of liver is common in some of the lower animals, especially in some embryonal forms of fish. The manner in which the cystic diseases of the kidney are formed by a congenital malformation is not known. It is probably due to failure of the two anlagen of the kidney to unite, and the consequence is that the tubules have no outlet, and they eventually become cystic. Clinically, it is a remarkable phenomenon that these patients live to such a ripe age. It proves the enormous compensatory power of the human body.

DR. LARKIN: I recall very well the work of Dr. Moschcowitz on congenital cystic kidney, and also on cystic liver. I think his idea at that time, *viz.*, that it is a congenital embryonic defect, has never been refuted. When studying congenital cystic kidney in the adult, we do not have to confine ourselves to the adult human, because it is not at all unusual in the lower animals, particularly in the pig. At the museum in the College we have several specimens of congenital cystic kidney in the pig. They correspond histologically to the same condition in the human. The most remarkable thing about all of these cases is the fact that the individual lives for so many years. The last bilateral cystic kidney that I had an opportunity to look at was in a man seventy years of age, on whom we had done a large number of chemical blood examinations, with normal findings. The patient finally died of an intercurrent condition, and showed just what has been shown here. This illustrates the possible failure of chemical examinations of the blood in which the kidney is supposed to be non-functioning. These kidneys, although surprisingly malformed, when examined microscopically, show a great deal of functioning kidney tissue in

different parts. We find normal glomeruli, and fairly normal tubules in kidneys which have these malformations and embryological defects, and still the kidney is functioning. An interesting anomaly associated with congenital cystic kidney is the one which Dr. Moschowitz mentioned, a child with six fingers, six toes, and spina bifida. Only the other day I had an opportunity of looking over an anencephalic monster which was rather unusual. It might be designated as a case of neuter gender. It was a child born at the Maternity Hospital which showed no genitalia at all. There was simply a little pedunculation in the region of the penis; there were no testicles and no evidence of sex. These congenital anomalies were manifest on external examination, and on further examination other congenital defects of the viscera, such as cystic disease of the kidney, will probably be found.

DR. TOW: I should like to add a few words about treatment. You can not do anything for these cases medically, except possibly treat the condition as one of chronic nephritis. Roysing, a Scandinavian surgeon, some years ago advocated puncture of these cysts, believing that if they grew to large size, they might cause pressure symptoms; and he has reported some good results from this procedure. But in this country there has been a great deal of discussion about his operation, and a number of surgeons claim that this procedure does no good. Nephrectomy is, of course, absolutely contraindicated, as the condition is practically always bilateral.

DR. MACNEAL: It seems to me that an important thing in connection with congenital polycystic kidney is to exhibit these specimens to the surgeons. It is an extremely dangerous thing for the patient when a surgeon not familiar with this condition undertakes an exploratory laparotomy on one of these cases. Some of us have seen the occasional unfortunate results of that sort of thing. We should show such specimens to every person doing operative work, so that he will recognize the condition when he comes upon it at an exploratory operation.

As a second point I wish to raise the question whether the condition in the child's case is actually the same as in the others. Usually these individuals with congenital polycystic kidney go on to old age. The child died with evidences of kidney insufficiency, and there is evidently a good deal of inflammatory fibrous tissue in the kidney. I am inclined to question whether we are dealing with the same entity in the case of this infant.

DR. TOW: We considered that the infant's kidneys were congenital cystic kidneys, and that death was caused by edema of the brain and edema of the lungs, which I attempted to explain on the ground that the heart was not able to carry on its work because of the tremendous amount of connective tissue in the kidney structure. Whether the kidneys of the infant in Case 1 and those of the adult in Case 2 represent two separate conditions I am unable to say definitely, but we considered them as one. Grossly, there seems to be considerable difference in the two specimens, and microscopically one sees a great increase in the connective tissue in sections of the infant kidney. It may be explained perhaps on the basis of the theory of maldevelopment. In the adult kidney more fusion between the secreting and excreting elements of

the embryo took place, and as a result we had more of a picture of a normal kidney with little interference in kidney function. In the infant kidney, on the other hand, little union between these two structures took place and, as a result, but little kidney structure was formed, and the kidney resembled more the embryonal type.

THE URIC ACID CONTENT OF SPINAL FLUID

ADOLPH BERNHARD, B.S.

(From the Pathological Laboratory, Lenox Hill Hospital, New York City)

In 1916, Leopold and Bernhard¹ published the results of the first complete investigation of the non-protein constituents in the spinal fluid of children. They state that in normal spinal fluid there was only a slight positive reaction for uric acid in a few cases, but in not a single instance was there sufficient uric acid present for a quantitative estimation. In these determinations the Benedict² modification of the Folin and Denis method was employed. At about the same time Myers and Fine³ reported a series of cases of nephritis in which the spinal fluid was examined for its non-protein nitrogenous constituents. In the fifteen cases which they reported, thirteen showed retention of urea, and in eight there was a retention of creatinine in the blood, with corresponding increases of the same constituents in the spinal fluid. Their figures for the uric acid content of the spinal fluid varied between 0 and 1.5 mg. per 100 c.c. The amount of uric acid in the spinal fluid according to these authors is about five per cent. of that found in the blood. Kahn and Neal⁴ in 1917 reported the results of their studies on the non-protein nitrogenous constituents of the spinal fluid, and found that uric acid was either absent or was present only in minute traces.

Cushing⁵ and his co-workers have made a careful study of the secretion of the cerebro-spinal fluid, and found it to be chiefly secreted by the choroid plexus, the cells of which are relatively impermeable to the passage from the blood stream of drugs and substances such as bile pigments.

From the results reported up to the present time, it would appear that uric acid does not pass readily through the choroid plexus into the spinal fluid of normal individuals.

It is important to note here that the methods employed by previous workers in the determination of uric acid in low concentrations required relatively large amounts of material, and the accuracy of the method was open to question. Precipitation of uric acid with silver magnesia mixture is not quantitative when small amounts are present.

The results obtained in this report, using the new procedure devised recently by Benedict⁶ for the determination of uric acid, show conclusively that uric acid is a normal constituent of the spinal fluid and seems to be increased in infections. Briefly, the method is as follows:

To 2.5 c.c. of spinal fluid is added distilled water to 10 c.c., 4 c.c. of 5 per cent. sodium cyanide and 1 c.c. of the Benedict arsenic tungstic acid reagent. The mixture is placed in boiling water three minutes, and after cooling for three minutes it is compared in the Duboscq colorimeter with a standard solution of uric acid (5 c.c. equals .02 mg. uric acid) treated in the same manner. The colors obtained are very easy to compare.

In the table the results of the examination of fourteen spinal fluids for their uric acid content are given. The sugar concentration is also given. The uric acid varies between 0.3 mg. and 4.8 mg. per 100 c.c. The latter figure was obtained in a case of tuberculous meningitis three hours before death. It will be noted that the urea nitrogen was also increased. Unfortunately, the blood was not obtainable for comparison. Previous examinations of this fluid showed a uric acid content of 1.2 and a sugar content of 0.010 per cent.

In two cases of encephalitis the uric acid was increased 1.2 and 2.0 mg., and in one case of chorea before treatment, the uric acid was 1.0. In the three cases of syphilis, the uric acid was low. The uric acid content of the spinal fluids of children seems to be somewhat higher than that of adults. The sugar content was determined by the Folin⁷ copper method, the same procedure being used as for blood. The sugar content of normal spinal fluid varies between 0.051 and 0.112 per cent., the average being 0.073, which is in agreement with the figures obtained by others.

History No.	Sex	Age	Uric Acid	Sugar as Dextrose	Cell Count	Globulin	Wassermann	Diagnosis; Remarks
7203	M.	9	Mg. per 100 c.c. 0.62	Per cent. 0.051	—	—	—	Chorea
7442	M.	12	1.00	0.065	—	—	—	Chorea
7339	F.	67	0.30	—	40	neg.	neg.	Syphilis
7666	F.	5	0.62	0.083	10	—	neg.	Acute Poliomyelitis
7953	M.	21 mos.	1.25	0.010	—	—	—	Blood Uric Acid 2.4 mg. per 100 c.c.
"	Nov. 11	"	1.26	0.017	250	—	—	Nov. 19 '22.
"	Nov. 23	—	4.8	9.020	—	—	neg.	Tuberculous Meningitis
								Thec. found in Spinal Fluid Autopsy
								Urea N. 40 mg. per 100 c.c.
								Creatinine 1.6
8198	M.	44	0.43	0.062	30	—	neg.	Syphilis
8874	M.	43	0.46	0.062	neg.	neg.	neg.	Blood Uric Acid 4.8 mg. per 100 c.c.
8519	M.	40	1.50	0.020	2610	—	neg.	Syphilis; Optic Atrophy
"	Dec. 7, '22	—	2.00	0.035	—	—	—	Dec. 5 '22. Acute Polioencephalitis. Died
								Blood Urea N. 22
								Uric Acid 4.3
								Creatinin 1.3
								Sugar 0.162
P. 303			0.49	0.083	neg.	neg.	—	Fracture of Skull
								Concussion, Coma
8785	M.	12	0.72	0.071	—	—	—	Chorea
8893	M.	53	0.62	0.107	20	—	neg.	Pulmonary Tuberculosis
9103	F.	11	1.20	0.062	neg.	neg.	neg.	Encephalitis
9008	M.		0.30	0.112	10	neg.	neg.	Sinus Thrombosis
9025	F.	9	0.44	0.055	—	—	—	Chorea
								Blood Uric Acid 2.5 mg. per 100 c.c.

The sugar content was decreased considerably in the two cases of infection where the uric acid was increased. A similar observation was reported by Leopold and Bernhard in six cases of meningitis. In this series, the uric acid was also demonstrable in three cases of tuberculous meningitis.

While the number of cases here reported is small, it may be concluded that uric acid is a constituent of normal spinal fluid and seems to be increased in infections. It may be easily determined by Benedict's method.

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GIANT CELL SARCOMA AND CARCINOMA IN THE SAME BREAST

D. S. D. JESSUP, M.D.

The case which I have to report is from the Service of Dr. C. A. McWilliams at the New York Skin and Cancer Hospital. This specimen was from a patient thirty-four years old, whose personal history was in the main negative. She had been married for fifteen years, and had had seven children, five well, and two had died, stillbirths, due to difficult deliveries. She had nursed all of her babies. There had been no previous trouble with her breast. The family history was negative. There was no history of syphilis, tuberculosis, or skin disease in the family.

The present illness, for which she was admitted to the hospital, was after the birth of her seventh baby, four months ago. She had been nursing the child, and was nursing it up to the time of her admission. Two months previous to admission she had bruised her breast against a bedpost, with pain in that region for a short time, though there was no redness or pain at first. A few days later the patient noticed a hard and movable swelling. The tumor has remained about the same size; has never been tender or inflamed, is painless, and there has been no interference with nursing the baby. She has never had any previous history of breast trouble.

On admission to the hospital physical examination showed the heart, lungs, extremities, etc., were negative. The right breast was normal. The left breast was firm, and showed a firm, hard, small mass about the size of an egg in the upper medial quadrant, not attached to the skin or underlying muscles, and not tender. There were palpable glands in the axilla. On account of the age of the patient and the fact that she was nursing the baby, it was thought best to determine the character of the tumor by frozen section before doing a radical operation. This tumor was removed and sent to the laboratory. The tumor felt before operation was a mass about 5 cm. in diameter, sharply encapsulated, and on section showing areas of degeneration and hemorrhage. In some portions it was almost cystic. There was in the section a spindle cell growth resembling a spindle cell sarcoma, and on the basis of that diagnosis the rest of the breast was removed. Paraffin sections later showed what did not appear in the frozen sections; in the main encapsulated tumor there were quite a number of giant cells mixed in with the spindle cell growth, giving the appearance of a giant cell sarcoma. Paraffin sections were also made of the rest of the breast, which on section was exuding milk and showed the ordinary appearance of a lactating breast. In the axillary tissue a number of enlarged hard nodes were found. In cutting the rest of the breast we were surprised to find areas of scirrhous carcinoma with nests of typical epithelial cells, and we found this same growth in the axillary nodes. This was not suspected from the gross appearance, as it was apparently a diffuse condition. Later, as a control, other sections were cut, and outside of the original encapsulated giant cell sarcoma a few areas of giant cells were mixed in with the carcinoma so that we have apparently not only a discrete giant cell sarcoma in a breast in which there evidently had been a carcinoma at the same time, but also areas of a sarcoma mixed in with the carcinoma.

Two years ago a tumor was shown before this Society, a giant cell sarcoma with metastasizing new growth into the axillary nodes, and on the same evening Dr. Wilensky showed a tumor which he called a carcino-sarcoma, which showed the same appearance in the breast of a giant cell sarcoma and a carcinoma. At that time there was a great deal of discussion by the Society as to whether the case of the tumor from the Skin and Cancer Hospital was primary in the breast, or whether it was metastatic from a tumor in the bone. On a suggestion made at that time the patient was subjected to x-ray of the bones, and no tumor was found. Whether this particular tumor should be considered as a metastatic tumor, that is, a sarcoma possibly from some bone condition, or whether it should be considered a separate tumor superimposed on a carcinoma, I should be glad to have the Society discuss.

Discussion:

DR. MARTLAND: I did not hear the first part of the paper. I should like to ask how large the area was that showed the picture of giant cells of the foreign body type. That part of the tumor to my mind is nothing but an inflammatory lesion, similar in every way to benign giant cell tumor of bone. Whether you have a carcinoma of the breast mixed up in a chronic mastitis or some other inflammatory lesion I would not like to say without seeing the gross specimen and the microscopic slides. The picture thrown on the screen shows a great number of foreign-body giant cells with a fibroblastic stroma showing apparently an absence of mitoses. I should not consider such a lesion sarcoma. It seems to me we have a carcinoma of the breast and possibly some inflammatory lesion.

DR. WOOD: I had an opportunity to look over these sections. I have examined a good many breasts in my time, and I have never seen an inflammatory lesion which looked like the one shown on the screen. The picture is one which you see in the ordinary central giant cell sarcoma of the bone. There are occasional mitoses in the connective tissue of the sarcomatous fraction. I do not think there is anything extraordinary about this specimen except the unusual coincidence of these two types of growth in the same patient. We occasionally see giant cell sarcoma of the breast, and carcinoma every day; the queer thing is that chance should have put the two things into one piece of tissue at the same time. The breast carcinoma is evidently very old, but the interesting thing is that the metastases in the nodes carry the striking alveolar quality which the slides show. I have two specimens in which there are two types of carcinoma in the breast which metastasized separately into the same node, one alveolar, and the other scirrhous in type. I do not think it is highly malignant, but any ordinary inflammatory process can be excluded. The idea that all the giant cell sarcomata of the bone are inflammatory has never appealed very strongly to me. About the time that you have made up your mind that they are all inflammatory, one recurs in the lung, and the patient dies with a tumor of exactly the same morphology as those that are apparently benign.

DR. JESSUP: In regard to the question that was asked, this tumor is made up of entirely the same type of new growth, encapsulated, showing scanty giant cells, and there are mitoses present. I think if you will look at the slide under the microscope you can get the idea better. I came a little bit late, and was unable to set the slides up before the meeting. There is one section of this tumor, and another section shows also the same giant-celled growth mixed in with the carcinoma.

DR. MANHEIMS: I saw a section with Dr. Rohdenburg the other day where a sarcoma and a carcinoma occurred in the same uterus, the two being in separate portions of the uterus.

A SKIN CANCER FOLLOWING EXPOSURE TO RADIUM

WARD J. MACNEAL, PH.D., M.D., AND GEORGE S. WILLIS, M.D.

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(Abstract *)

Dr. Willis, aged forty-six, developed a squamous-cell carcinoma on the ball of his right thumb in the fall of 1922. He had worked with Roentgen rays from 1905 to 1917 but always with careful protection by lead gloves. From 1912 to June, 1920, he used radium and from 1915 to 1920 he handled amounts of 200 mg. or more of radium in individual tubes daily, without precautions for personal protection. The glass tubes containing the radium were habitually picked up between the thumb and fingers of the right hand.

Various changes in the skin, which may be ascribed to the exposure to radium, began to be observed late in 1918 and since early in 1920 the skin changes have required constant care. The skin first became curiously numb and later tender and sore, with a burning sensation, sometimes an ache and often neuralgic pain. Objectively, the surface became rough and harsh with fine horny spines, hyperkeratoses, and callosities. Fissures have been almost constantly present.

The carcinoma was recognized on November 3, 1922, and the thumb was amputated November 4, 1922. The new growth infiltrates deeply and is of a malignant type. The skin at a distance from the carcinoma shows various structural alterations which resemble somewhat the changes described by Gassmann and by Unna in Roentgen-ray dermatitis.

Photomicrographs were demonstrated.

* The full paper appears in *Jour. Am. Med. Assn.*, 1923, lxxx, 446.

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Discussion:

DR. CORNWALL: Dr. MacNeal stated that at one period there was loss of power in the left arm. Has that persisted, or was it just a transitory feature? I should also like to ask if there was any pain preceding the numbness.

DR. WOOD: This is an extraordinarily interesting case. There is no question that the handling of radium will produce carcinomata in the susceptible human being, just as well as x -ray will. There is probably no difference in the effects of the two. The biological effects are the same, as the killing of mouse tumors takes place with the same multiple of an erythema dose with either agent. I think Dr. MacNeal's explanation of the few cases of radium burns is the right one, that there are fewer people who have handled large quantities of radium, simply because there have not been large quantities to handle. The x -ray lesion is seen in men who have worked for a great many years with it, and have developed those peculiar warty keratotic conditions of the skin. After a certain period of time has elapsed in the susceptible, the tumors appear, but not all keratoses become cancerous. It seems to me a condition of an exquisite chronic inflammatory process like the one we produce in mice when they are painted with coal-tar for a year. After that time a good many tumors appear.

It is very difficult to make a diagnosis on some of these x -ray specimens in man. Deep penetration down the fissures often occurs when the process is still benign, and it is probably safer to amputate than to pass up the matter. It has been said that radium will cure these x -ray epitheliomata. Radium will cure the keratoses but not an epithelioma. These tumors are exceedingly malignant and twice I have seen a sarcoma develop secondary to long continued x -ray irradiation. In rats also sarcomata have been produced by long continued radiation of the skin and subcutaneous tissue. Rats do not easily develop carcinoma.

DR. WILLIS: In reply to the question about pain, yes, it was always very painful. That was the first symptom noted. It gradually increased. The left arm has improved a great deal within the last year or so.

DR. MACNEAL: In regard to the weakness of the left arm, I thought it should be stated in the paper as indicating a possible independent neuritis, which might offer an explanation of the numbness; but it does not explain it to my mind. I do not believe the failure of strength in his arm was due to radium, but the fact that he had that weakness in his left arm may, possibly, have had some connection with the numbness.

This presentation may, perhaps, have very little value to those who are thoroughly expert workers in x -ray and radium. The experts know that these two agents do exert similar influences on tissues and that somewhat the same sort of results are to be expected from their use. But when you attend a High School graduation and observe a pupil dressed as Radium coming in to drive cancer out of the universe, you begin to think that there is a necessity for emphasizing the fact that radium is not wholly a benign and harmless agent which can be employed in an unintelligent and careless manner. If you can show somebody who has gotten cancer from using radium, such a demonstration will have more telling effect with the uninitiated than if you argue from scientific grounds that there are the same dangers in the use of radium and x -ray.

DR. WOOD: May I add another word to this discussion? One of the most deceptive things occurs in the use of protective lead rubber and articles of that sort, and that is that in the average lead rubber that one gets about one half of the x -ray goes through. Most x -ray men believe that if they put on a heavy pair of lead rubber gloves they are fully protected, but an astonishing amount of x -ray goes through, so that the protective lead rubber does not really protect, and some of the trouble we are having with patients is due to the fact that this rubber that is sold as very good protection as a matter of fact gives very little. When we get a little more careless in the use of x -ray we will begin to expose ourselves a little more. People who are doing therapeutic work should be sure that their screens are fully protected, to see that they are not getting more than a quarter of the dose. I know a man who got a full erythema dose on his face the other day.

THE COMPLEMENT FIXATION TEST IN TYPHOID CONVALESCENCE

A. L. GARBAT, M.D.*

About eight years ago the author showed that practically all patients with typhoid fever develop complement fixation bodies in their blood sooner or later during the course of the disease. At the same time the writer found that people inoculated against typhoid fever develop a positive complement fixation test only exceptionally and for a very short time. No systematic report exists in the literature referable to the complement fixation reaction during convalescence. The present statistics include such tests made on 160 typhoid patients.

* For detailed statistics, see Rockefeller Monograph, Typhoid Carriers, 1922.

TABLE I

Time of Examination (after normal temp.)	Cases Examined	Number Positive	Degree of Positive				Per Cent. of Positive
			4+	3+	2+	1+	
2d month (5, 6, 7 and 8 weeks) after normal temp.	22	16	13	1	1	1	72.7
3d month (9, 10, 11 and 12 weeks) after normal temp.	114	67	43	5	9	10	54
4th month (13, 14, 15 weeks)	14	8	5	0	0	3	57
	150	91	61	6	10	14	60

It is noted that as high as 54 to 57 per cent. of the patients still gave a positive complement fixation test four months after the active stage of typhoid fever, and in two thirds of these the reaction was very strong (4+).

These patients were re-examined several months later with the following results:

TABLE II

Time of Examination (after normal temp.)	Cases Examined	Number Positive	Degree of Positive				Per Cent. of Positive
			4+	3+	2+	1+	
5th month (17, 18, 19, 20 weeks) after normal temp.	41	24	9	7	4	4	58
6th month (21, 22, 23, 24 weeks) after normal temp.	119	49	20	7	12	10	41
	160	73	29	14	16	14	45

From these two tabulations it is evident that in about 30 per cent. of typhoid patients the complement fixation bodies disappear from the blood by the second month after the onset of normal temperature. During the third, fourth, and fifth months after convalescence, an additional 10 to 15 per cent. of the patients lose this reaction. At the end of a half year 40 per cent. of the patients still show a positive complement fixation reaction, while at the end of nine months this becomes 25 per cent.

These findings bring up the question why the complement

fixation antibodies persist in some patients long after convalescence, while in others they disappear soon after or even before the onset of normal temperature. An analysis of our cases was therefore made from a clinical standpoint in order to determine any factors which might possibly account for these variations.

1. *Blood Culture Findings:* It is well known that in animals antibody formation is most rapid and marked when the intravenous method of immunization is employed. It was, therefore, considered probable that patients with a persistent positive blood culture would be the more likely ones to continue with a positive complement fixation test. It was found, however, that one can not consider a positive blood culture as the indicator of a future persisting complement fixation test.

2. *Length of the Fever Course:* It was felt that the longer the fever existed, the more likely was it that live bacteria were in action and consequently antibodies were being stimulated. It was found that the patients who ran a longer fever course appeared more prone to develop a lasting complement fixation test. Still, the length of the fever course alone can not be considered the deciding factor, as there were many patients with a prolonged fever who gave a negative complement fixation test, and some who ran a very short illness who nevertheless showed many fixation antibodies.

3. *Severity of Disease:* The severity of the illness of the patients was considered entirely separate from the length of the disease. It seemed as if the more severe cases showed a greater percentage of positive complement fixation tests. On the other hand, severity of disease alone can not be taken as the criterion, since it is seen that there are many very mild cases which developed lasting complement fixation tests, and *vice versa*, many sick cases which were negative early during convalescence.

4. *Relapses and Recrudescences:* The relationship which relapses and recrudescences bear to the stimulation of complement fixation antibodies was considered apart from either the length or severity of the illness. It was thought that the patients who

have such set-backs usually go through a longer and more severe infection, and consequently complement fixation tests would be more prone to remain positive for a prolonged period of time. Of seventeen patients who suffered *relapses*, sixteen were positive for two to three months, and fourteen continued positive for six months or longer after normal temperature. It is interesting to note that the only patient who was negative had three relapses and finally died with typhoid bacteria still in the gall bladder (possibly due to a complete lack of immunizing power). Of fourteen patients with *recrudescences*, nine showed a lasting complement fixation test. Thus, out of thirty-one patients with either a recrudescence or a relapse, 25, or 80 per cent., continued with abundant complement fixation antibodies for many months after convalescence.

5. *Complications*: It was assumed that patients with true typhoid complications, *i.e.*, those caused by the *B. typhosus* and not by a secondary invader, have a greater number of bacteria or toxins to cope with, and therefore would be more likely to combat the increased infection by the production of a greater number of antibodies. Of thirty-one cases which had a complication due to the typhoid bacillus, twenty-three, or 74 per cent., showed a positive fixation test which continued for many months after complete convalescence.

TABLE III

Complement Fixation Test

	Number Positive.	Number Negative.
Pleuritis	1	
Typhoid Spine.....	1	1
Neuritis	1	
Cholecystitis	5	2
Parotitis	1	
Hemorrhage	4	1
Appendicitis	1	
Nephritis	2	
Periostitis	1	2
Psychosis	1	
Phlebitis	1	2
Pneumonia	1	
Perforation	3	

Carriers: The relationship between the typhoid carrier state and the presence of complement fixation bodies is of extreme importance. The findings in the temporary and permanent carriers will be discussed separately.

For *temporary* carriers, the statistics are based upon patients in whom the bacteria in the urine or stool persisted for some time. Cases with an occasional presence of the typhoid bacillus in the excreta were almost the rule, and were, therefore, not included in the analysis.

In all of ten *urine carriers*, complement fixation persisted strongly positive; in four, for two to three months, and in six, for four to six months after convalescence; in nine of the urine carriers the complement fixation test remained positive for months after the carrier state cleared up.

Of three *feces carriers*, two were positive for four months, and one negative early during convalescence. Contrary to expectation, the latter became a permanent bile carrier.

Of nineteen patients with *typhoid bacteria both in the urine and stool*, fifteen continued to show strong complement fixation for six months and longer after convalescence, while four were negative two months after normal temperature. The complement fixation tests remained positive after the bacteria had disappeared.

Taking all these classes together, it was found that out of thirty-two temporary typhoid carriers, twenty-seven, or 85 per cent., showed a constant and strong fixation reaction, while in 15 per cent. the fixation antibodies disappeared early, although the carrier stage continued. *Vice versa*, in almost all of the temporary carriers with a strongly positive complement fixation, the antibodies remained demonstrable long after the bacteria had disappeared.*

As for the *permanent or chronic carriers*, some references are found in the literature regarding their complement fixation bodies. Schöne reports the findings in three carriers, only two of whom were chronic carriers. The reaction was positive in one for ten and one half years, and negative in the other for two years.

* It was difficult to determine how long the test remained positive, as all the patients were transferred to ports of debarkation.

Henderson-Smith (reported by Ledingham and Arkwright, "The Carrier Problem," page 125) demonstrated these bodies in the sera of two carriers, both of whom gave negative Widal tests.

Of the writer's four probably permanent bile carriers of eight to nine months duration, only three continued strongly positive. The fourth was negative two months after normal temperature. In one patient who was a very marked bile carrier and who was cured by cholecystectomy four months after the acute illness, the complement fixation bodies were still present in great numbers eight months after operation.

Three chronic carriers were examined by the author for Lt. Col. Nichols with the following results:

(1) Typhoid fever in January, 1918; carrier condition resulted; cholecystectomy in November, 1918, cured; complement fixation strongly positive in February, 1919.

(2) Typhoid fever in 1910; carrier condition resulted; cholecystectomy in 1918; carrier condition continued; complement fixation strongly positive in February, 1919.

(3) Typhoid fever in 1905; carrier condition resulted; cholecystectomy in 1918; carrier condition continued; complement fixation \pm in February, 1919.

Resumé: From an analysis of the above discussions, the writer has formed the conclusion that the fixation test is dependent directly upon the number of typhoid bacteria the patient is infected with and the length of time that they remain in the system. The greater the number or the longer the time, the stronger and more lasting will the test be. A large number of bacteria may or may not however mean a sick patient, a long disease, a relapse, a complication, or a carrier state. Other factors, such as the virulence of the particular bacillus, the resistance of the individual, etc., which we can not estimate, bear additional influence.

Therefore, one can not foretell whether a particular patient will persist with a complement fixation test or not. If from the clinical course of the disease or the laboratory findings one has reason to feel that the patient is infected with a large number of

bacteria and over a prolonged period of time, one may assume that the complement fixation test will continue positive for a long time, even years after convalescence. This is usually the case in long continued illness, with relapse or complication or carrier condition. Reversely, the continued positive test may be the first indication of the systemic response to a large number of typhoid bacteria.

Discussion:

DR. NORRIS: I would like to compliment Dr. Garbat on his work, and I should like to ask if he has had the opportunity to make microscopical examinations of the livers of the known typhoid carriers. Dr. Garbat brought out the point that when the gall bladder has been removed the patient may be a liver carrier. Dr. Koch I think was the man who brought out that point. I myself have never had the opportunity of examining a typhoid carrier, and ask if he has run across definite microscopical lesions in typhoid carriers in the liver or in the kidney.

DR. GARBAT: The only thing I found in the liver of these carriers was a round cell infiltration in small areas.

A COMPARATIVE STUDY OF THE KAHN AND WASSERMANN TESTS, BASED ON FIVE HUNDRED CASES

(From the Laboratories of The Lenox Hill Hospital, New York City)

PERRY J. MANHEIMS, M.D.

R. L. Kahn¹ has recently described a quantitative precipitation reaction for the diagnosis of syphilis. Further studies and reports have been published by Keim and Weil,² Young,³ and Ide and Smith.⁴

The test is somewhat similar to the precipitation reactions devised by Sachs and Georgi,⁵ Meineke,⁶ and others. All these investigators have found that when a definite amount of an alcoholic antigen made from beef heart properly diluted with saline is added to luetic serum, a reaction occurs, as shown by the formation of a precipitate. A non-syphilitic serum in contrast does not give the reaction. The various precipitation reactions are

no doubt based on the results of the studies by Michaelis,⁷ who showed that by adding inactivated luetic serum to a properly diluted alcoholic antigen made from syphilitic liver and incubated for five hours at 37° definite flocculation occurred with luetic serum, and none with normal serum.

The antigens used in the present series were prepared according to the method described by Kahn. Fresh beef heart, freed from fat, fibrous tissue and blood vessels was ground in a meat chopper, then spread on a large porcelain dish and dried by means of an electric fan. About twenty-four hours was required to thoroughly dry the meat. This dried material was then finely ground in a coffee grinder. The resulting substance is a dry, light brown powder. Fifty grams of this was then extracted with ether in a 500 c.c. Erlenmeyer flask. After twenty-four hours' extraction in the icebox, the supernatant ether was poured off and fresh ether added. This was repeated daily until the supernatant ether was colorless, when the last ether was poured off and the ground muscle thoroughly dried and freed of the ether.

Five c.c. of absolute or 95 per cent. alcohol was then added for each 1 gm. of dried material and the mixture allowed to extract for nine days in the icebox and one day at room temperature. The alcohol was filtered off and an aliquot amount cholesterinized by adding cholesterin in the proportion of 4 mg. per c.c. For the test, the alcoholic and cholesterinized antigens were diluted with two and three parts of 0.85 NaCl solution respectively.

An important point to be noted is the method of making the diluted antigens. The salt solution must be added rapidly to the antigen in a test tube or small graduate, and then immediately mixed by inverting the tube. It is not necessary to shake. If the antigen is not properly mixed with the saline, precipitation may occur. The resulting mixtures should be quite milky and opalescent, the cholesterinized antigen more so than the alcoholic. The diluted antigens are kept at 37° C. until used.

Although Kahn stated that he had employed antigens im-

mediately after diluting with saline solution, as well as two weeks after diluting, with approximately the same results, we have found, as did Keim and Weil, that older antigens (those kept in the incubator a week or more after being diluted) did not seem to be as sensitive as those used the same day.

For the test, serum inactivated for one half hour at 56° is used just as in the Wassermann test, and the antigens added. Only two tubes are necessary for each test (ordinary Wassermann tubes being used), one for each antigen. The unused diluted antigens are controls.

We have been using as originally suggested by Kahn, 0.3 c.c. serum and 0.05 c.c. antigen, although he also says that as long as the proportion of 6 to 1 is maintained any quantities may be used. This is of advantage when only small amounts of patients' blood are obtainable. After the addition of antigen to the inactivated serum, the tubes are vigorously shaken for about three minutes and placed in the incubator at 37° . Strongly positive sera may sometimes be read in a few hours, but we have found that the best readings are obtained after about eighteen hours' incubation. The tubes are placed in the incubator late in the afternoon and read the next morning.

Negatives are clear, and the strongly positives show a marked flocculent precipitate, suspended in the liquid medium. The four plus shows either one or more large clumps, the three plus, smaller clumps, the two plus and weaker positives, granules of lesser size. The weaker reactions are best seen by slanting the tubes. The tubes should not be shaken while reading because there is sometimes a certain amount of sediment, more marked in the cholesterinized tubes, which should not be confused with a weak positive. The best method of reading seems to be by holding the tubes against an electric light.

The following data are based on 500 tests done parallel with the Wassermann reaction. The sera were picked indiscriminately, and the readings were not influenced by the Wassermann results, as they were made at different times, without knowledge of the results of the Wassermann fixation.

Alcoholic and cholesterinized guinea pig heart antigens with icebox fixation, and a sheep blood hemolytic system were used in the Wassermann fixation.

In order to simplify in tabulating, we have grouped the negative and plus-minus readings under negative, and the three and four plus under one heading. In 389 cases where the alcoholic antigen Wassermann was negative, the Kahn was negative in 97 per cent., and in 374 cases where the cholesterinized antigen Wassermann was negative, the Kahn was negative in 92 per cent.

TABLE I

389 Negative or Plus-Minus Wassermann Alcoholic Antigen Results With Kahn Test Alcoholic Antigen		374 Negative or Plus-Minus Wassermann Cholesterinized Antigen Results With Kahn Test Cholesterinized Antigen	
Negative or Plus-Minus.....	378		352
1 Plus.....	6		11
2 Plus.....	3		8
3 Plus.....	0		2
4 Plus.....	2		1

In the total of 500 cases, one was negative with both Wassermann antigens and four plus with both Kahns. This was a Hospital case, and the Laboratory slip accompanying the blood stated: "Observation, Lues Suspect." We had intended repeating the test the following week but were unable to do so as the patient had left the Hospital. The other instance where the alcoholic antigen Wassermann was negative and the corresponding Kahn was four plus was a treatedluetictic case and the results were a plus-minus and four plus Wassermann and a double four plus Kahn. The two instances where the Kahn was three plus were treated cases of lues. As the chart shows, practically all of the cases where the Wassermann was negative and the Kahn one or two plus were treatedluetictics.

But if we analyze the next table showing discrepancies from a one plus Wassermann, we notice that half of the negative or plus-minus Kahns were treatedluetictics, and the proportion of these is larger than the Kahns which gave a stronger reaction than the Wassermann.

TABLE II

Cases where Wassermann was Negative and Kahn Positive

	Wassermann		Kahn		Diagnosis
	Alco- holic	Choles- terinized	Alco- holic	Choles- terinized	
1.	0	4	1	4	Treated Luetic
2.	0	0	4	4	Observation Lues Suspect
3.	0	0	1	2	Carcinoma Cervix
4.	0	2	2	3	Infected Finger
5.	P.M.	4	4	4	Treated Luetic
6.	0	0	0	1	Treated Luetic
7.	0	0	0	2	Treated Luetic
8.	0	0	2	0	Pyosalpinx
9.	0	2	1	2	Treated Luetic
10.	0	1	2	2	Treated Luetic
11.	2	P.M.	2	2	Primary Lues Nov. 17 Dec. 12
	3	2	0	0	
12.	0	0	0	3	Treated Luetic
13.	0	0	0	2	No Diagnosis
14.	0	P.M.	0	1	Treated Luetic
15.	0	0	0	1	Old Luetic.
16.	0	0	0	1	Chronic Appendix
17.	2	0	0	1	Treated Luetic
18.	0	0	0	2	Treated Luetic
19.	0	0	0	2	Treated Luetic
20.	0	0	1	1	Pleuritis
21.	0	0	1	1	Chronic Rheumatic
22.	0	0	1	2	No Diagnosis
23.	4	0	0	2	Treated Luetic
24.	1	0	0	1	Treated Luetic
25.	0	0	0	1	Neurasthenia
26.	1	P.M.	0	3	Treated Luetic
27.	0	0	0	1	Treated Luetic

TABLE III

Results With Kahn Test.

21 One Plus Wassermann Alcoholic Antigen		15 One Plus Wassermann Cholesterinized Antigen	
Negative or Plus-Minus..	17 (9 Treated Luetics)	10 (5 Treated Luetics)	
1 Plus.....	1 (Treated Luetic)	0	
2 Plus.....	1 (Treated Luetic)	4 (3 Treated Luetics)	
3 Plus.....	0	0	
4 Plus.....	2 (Treated Luetics)	1 (Interstitial Keratitis)	

Of the 23 cases which gave a two plus alcoholic Wassermann, the Kahn was negative, plus-minus or one plus in 16 instances, and two or four plus in 7 instances. Of the 26 cases which gave

a two plus cholesterin Wassermann, the Kahn was weaker in 14 of these, and in 12 cases was two plus or stronger.

TABLE IV

Results with Kahn Test.

	23 Two Plus Wassermann Alcoholic Antigen	26 Two Plus Wassermann Cholesterinized Antigen
Negative or Plus-Minus..	15 (9 Luetic Histories)	10 (5 Luetic Histories)
1 Plus.....	1	4 (2 Luetic Histories)
2 Plus.....	4 (4 Luetic Histories)	7 (4 Luetic Histories)
3 Plus.....	0	3 (1 Luetic History)
4 Plus.....	3 (2 Luetic Histories)	2 (1 Luetic History)

There were two anticomplementary sera in our series, one of these tests being repeated with fresh serum. The Kahn test was not influenced (see chart). Of course, we can hardly draw any conclusion from these few tests, but other workers have also noted that sera which are anticomplementary have no inhibitory influence on the Kahn test.

TABLE V

Sera Anticomplementary with Wassermann Test

	Wassermann		Kahn		Diagnosis
	Alco- holic	Choles- terinized	Alco- holic	Choles- terinized	
Oct. 24/22.....	A. C.	A. C.	0	0	Observation
Dec. 12/22.....	A. C.	A. C.	2	2	Lues Suspected
	Repeated with fresh serum.				
Dec. 18/22.....	A. C.	4	2	3	

There were 73 cases in which the alcoholic antigen Wassermann was positive, and 95 in which the cholesterinized antigen Wassermann was positive. With the alcoholic antigens the Kahn agreed with the Wassermann in only 40 per cent. of the tests, while 46.5 per cent. of the three and four plus alcoholic Wassermans were negative with the alcoholic Kahn antigen.

Of the 95 cases which were three and four plus with the Wassermann cholesterinized antigen, 64 per cent. gave the same

reactions with the Kahn, and 12 per cent. were two plus. Seventeen per cent. of these cases were negative or plus-minus with the Kahn cholesterinized antigen.

TABLE VI
Results with Kahn Test

	73 Three and Four Plus Wassermanns		95 Three and Four Plus Wassermanns	
	Alcoholic Antigen.	Per cent.	Cholesterinized Antigen.	Per cent.
Negative or Plus-Minus....	34	46.5	16	17
1 Plus.....	6	8	7	7
2 Plus.....	4	5.5	11	12
3 and 4 Plus.....	29	40	61	64

In our series the Kahn did not agree with the positive Wassermanns in the number of instances other investigators have reported.

In Kahn's preliminary communication, using two cholesterinized antigens, his results were:

227 positive Wassermanns gave	213 positive Kahns
	7 doubtful
	7 negative
90 doubtful Wassermanns gave	40 positive
	20 doubtful
	30 negative
802 negative Wassermanns gave	14 positive
	21 doubtful
	767 negative

Kahn in this article stated that in not a single instance did a serum giving a three or four plus Wassermann show a negative precipitation. We were unable to obtain such good results (see chart, Dec. 15).

TABLE VII

Comparison of Wassermann and Kahn Tests—Dec. 15, 1922

Wassermann		Kahn		Diagnosis
Alcoholic	Cholesterinized	Alcoholic	Cholesterinized	
4	4	0	0	Lues
4	4	0	2	"
0	1	0	0	Treated Lues
4	3	0	0	Lues Suspected
4	1	2	2	Lues
4	4	3	4	"
4	4	3	4	"
4	4	2	3	"
3	3	2	3	"
0	0	0	0	Old Treated Lues
0	0	0	0	Lues Suspected
4	4	1	3	Lues
0	0	0	0	Fracture of Femur
0	0	0	0	Fibromyoma

There were three other similar cases, one of which when repeated gave a three plus cholesterinized Kahn.

In Young's report of 5,000 examinations, two cholesterinized antigens were used:

1,055 positive Wassermanns gave	1,023 positive Kahns
	18 doubtful
	14 negative
304 doubtful Wassermanns gave	34 positive Kahns
	200 doubtful
	70 negative
3,721 negative Wassermanns gave	37 positive Kahns
	181 doubtful
	3,502 negative

In the report of Ide and Smith:

296 four plus Wassermanns gave	250 four plus Kahns
25 three " " "	35 three " "
28 two " " "	64 two " "

The fact that more of our results were not positive is possibly due in part to our attempt to try out the test. By this I

mean we did not pick our sera, and we found that hemolyzed and cloudy sera though four plus with the Wassermann did not give as strong Kahn readings as clear sera which were Wassermann positive. We also found that freshly diluted antigens were more sensitive than those diluted the week before. All these tests are included in our series and this no doubt accounts in part for our results. But I am unable to explain the discrepancies in tests made at the same time, when some four plus Wassermans were Kahn positive and others Kahn negative (see chart of Dec. 15). V. R. Mason⁸ quotes Vernes as saying, in speaking of his precipitation test (which is somewhat similar to the Kahn test), that a few sera fall into a common zone where it is impossible to distinguish a syphilitic serum from a normal serum by the flocculation reaction.

CONCLUSIONS

Aside from the preparation of the antigen, the Kahn test is far simpler than the Wassermann, both in actual technic and in substances necessary for the test, but with the exception of the three and four plus results, not nearly so easy to read. I must say that the reading of a plus-minus and the differentiation of a plus-minus from one plus is a great deal more difficult than in the Wassermann test.

The alcoholic Kahn antigen is not nearly as sensitive as the cholesterinized, and instead of an alcoholic and cholesterinized antigen, we would advocate the use of two different cholesterinized antigens. I believe that the alcoholic antigen has been generally discarded. Anticomplementary sera do not interfere with the test. The test does not seem to give false positive readings. Some strongly positive Wassermans are weakly positive or even negative with the Kahn test, but in quite a number of treatedluetics, the Kahn appears to be more sensitive than the Wassermann.*

The Kahn test should not be used to substitute or replace the

* The Wassermann tests were made by Miss Gertrude Hamilton of this Laboratory, to whom the author wishes to express his thanks for her cooperation.

Wassermann, but it seems to be an excellent additional test, especially in treated syphilitic cases, and I believe its chief usefulness at present to be along this line.

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Discussion:

DR. MOSCHCOWITZ: I would like to suggest to Dr. Manheims that he could get a better evaluation of the Kahn test if he made a parallel series on cases which could be either clinically or pathologically demonstrated as cases of syphilis. If you compare the Kahn test simply with the Wassermann test, you will not get much further, for you will have no standard to check up the value of the test as one for syphilis.

DR. EGGSTON: We have been using this test and have made 339 examinations and have compared them with the Wassermann test. We have arrived at practically the same conclusion as Dr. Manheims. We certainly would not want to replace the Wassermann with the precipitin test, but it is helpful in cases which are anticomplementary and in the cases which contain natural anti-sheep amboceptor. It is also of value in treated cases. Out of the 339 cases there were only seven cases where there was marked disagreement in the results. In those, four gave strongly positive Wassermann tests with a weakly positive Kahn, and there were three where the Kahn was slightly positive and the Wassermann was negative. We used the water bath because we found that precipitation takes place much more readily in the water bath than it does in the incubator. In line with Dr. Moschcowitz's suggestion, I wish to state that in cases of iritis and interstitial keratitis, where the eye men think syphilis the undoubted cause, we have gotten negative Wassermann and Kahn tests on the same sera. The Kahn test is certainly a much simpler procedure and less expensive than the Wassermann. No animals are needed in the Kahn test. Only two reagents are required; one can be made in the laboratory, and the other is the patient's inactivated serum.

We have made some studies upon the nature of the precipitate. The precipitate after washing with saline is alcohol-soluble, and this alcoholic solution of the precipitate seems to give a much more delicate complement fixation antigen than the cholesterinized alcoholic extract of beef heart. The antigen seems to be sensitized by having been mixed with a positive serum. Part of

the precipitate is ether-soluble. All of the antigen is acetone-soluble. The precipitate when mixed with complement will destroy the complement, just as any foreign precipitate substance, as powdered chalk, will destroy complement. By further studies of the precipitate the Kahn test may be of help in the solution of the mechanism of the Wassermann reaction. It would seem that the destruction of the complement in the Wassermann reaction is a physico-chemical process, destroyed by the absorption to the precipitate. The precipitate has a very low specific gravity. It is soluble in saline solution if heated to a temperature of 55 to 60°.

The Kahn test differs from the previously described precipitin test for syphilis in that the antigen is not greatly diluted. The antigen is diluted sufficiently to prevent the alcohol present from precipitating the protein of the serum that is added. In not diluting the antigen, Kahn maintains the precipitate develops more readily, which adds to the usefulness and delicacy of the test.

DR. MANHEIMS: To answer Dr. Moschowitz's question: in the table of December fifteenth all the cases marked "luetie" were known syphilitic cases where the Wassermann was sent to the Laboratory from the Luetic Clinic in the Hospital, and there you will find a discrepancy between the two tests. I am very glad to hear of the analysis of the precipitate by Dr. Eggston.

DR. GARBAT: Did I understand you to say that you used the precipitin obtained in the Kahn test for the antigen in the Wassermann test?

DR. EGGSTON: We dissolved the precipitin in alcohol and used it for an antigen in doing the Wassermann test, and got strong fixation of complement. This antigen was not anti-complementary, nor did it give non-specific reactions.

DR. GARBAT: We have always tried to standardize the Wassermann test, and I was interested to get in this morning's mail some antigen from Wassermann. He has been trying to standardize the Wassermann test in Germany, and to organize a central distribution center for antigen. He uses as antigen an alcoholic extract of luetic liver. He used to work with an aqueous liver antigen, and now he uses the alcoholic liver extract. He standardizes and ships it to various laboratories in Germany. Whether this antigen is any better than our cholesterinized beef heart antigen I do not know.

DR. CORNWALL: We have had a moderate amount of experience with the Kahn test at the City Hospital. Our tentative conclusions are about the same as Dr. Manheims'; that certain of the reactions are very difficult to read, namely, the one and two plus reactions. Strangely enough, in our first series we used some old sera, and in that particular set of reactions we had eleven positive Wassermans that were negative with the Kahn test. We thought, of course, that there might have been some error in our technique, though the technique is rather simple. In the last set that we did this afternoon the positives all agreed. The negatives have all agreed previously, but today we got one positive Kahn test in a case that gave a negative Wassermann with our cholesterinized antigen in the water bath and the crude alcoholic antigen in the icebox.

The work of Vernes was referred to. Several years ago he published

many of the facts that we are now reading in our literature. We have been working with the Vernes reaction for some time, and hope to have some conclusions soon. We have compared the reaction with the Wassermann, but we have confined the comparative studies to cases which we knew were clinically non-syphilitic, and to those which were historically syphilitic. Vernes has done one thing which Sachs-Georgi and Kahn have not done. He prepares his colloidal solution in a definite quantitative manner. He also dilutes his colloidal solutions in a constant manner, so that the turbidity is practically always identical. This is determined by a photometer. You can not do that with the Kahn test. Vernes always prepares his colloidal solution in a definite time, using a rotary machine at a definite number of rotations per minute, adding the saline to the antigen at a constant speed of one c.c. per minute. In this manner he always gets colloidal solutions of the same density. In addition, his method has one advantage over the Kahn and over the Wassermann in that his positive reactions can be read with greater range. The results are plotted with a curve, the rise and fall of which gives an index of the progress of infection and the influence of therapy. We find, however, with the Vernes test more frequently than with the Kahn that we have negative reactions when the Wassermann is positive, and for that reason we have tried to make as careful as possible clinical check on our cases so that we could determine the relative value of the reactions. I think the Kahn test has a definite advantage in this: It is a simple reaction and compares, according to the published results, fairly accurately with the Wassermann test; I do not believe that it is a dangerous procedure in the hands of untrained technicians, whereas I think we decided long ago that the Wassermann reaction should only be used by those who have been thoroughly trained in the fundamentals of serology. Certainly, with the Kahn test, so far as I am aware, non-specific reactions have not been reported. That is a very dangerous thing, but the Kahn test is free from that danger. It has that at least in its favor, and I feel that shortly we are going to use precipitation reactions much better standardized than the one that Kahn has given us.

A CASE OF MULTIPLE HEMANGIOMATA OF THE LIVER

WM. FRIEDMAN, M.D.

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Cavernous angiomas of the liver constitute one of the commonest post-mortem findings and are generally of little clinical significance. It has been assumed that they represent true malformations of the capillary blood spaces and are therefore to be classified in the general group of hamartomata. However, they so seldom give rise to symptoms, and are so rarely responsible

for death, that the condition about to be described probably falls outside the previous experiences of most of us. Furthermore, the association of enormous hemangiomata with a definite malformation in the venous system of the liver supplies additional suggestive evidence that the condition is primarily a true congenital malformation, rather than a neoplasm which had developed in post-natal life.

The case which I wish to present to the Society is that of a woman, thirty-three years old, a housewife, born in Hungary, who was admitted to the Mount Sinai Hospital in October, 1922, with the following history:

Her chief complaint was that of pain in the right upper quadrant of the abdomen for six months. This pain radiated into the right shoulder and flank. It was immediately relieved by lying down. There was moderate swelling of the right leg which disappeared when the patient was in a recumbent position. There was no loss of weight, and no gastric symptoms. There was polyuria and nocturia for two months before admission. The family history was irrelevant. Ten years before admission the patient had an appendectomy, two years before umbilical hernioplasty, and one year before right nephropexy.

The physical examination revealed a mass in the right upper quadrant of the abdomen about eight inches in its longest diameter, slightly tender and irregularly nodular, which appeared to be attached to the edge of the liver. It moved with respiration. The veins of the right thigh were somewhat enlarged. The blood count and blood Wassermann test were negative. Cystoscopy was negative.

The possibilities considered at this time were an abdominal tumor pressing on the vena cava, probably a new growth of the gall bladder, or the presence of a Riedel's lobe.

The operation performed by Dr. Beer showed a large cystic tumor mass about five inches in its longest diameter attached by a broad base to the under surface of the left lobe. The surface was irregularly nodular and covered by liver tissue. The cut section showed numerous large and small deep red areas varying from 0.5 to 2 cm. in diameter, which exuded a great deal of blood and presented a spongy appearance. A large vein was found running beneath the tumor which received branches from it. This was probably an extra hepatic vein. It appeared to run from the lower edge of the right lobe of the liver beneath the mass and into the inferior vena cava near the insertion of the other hepatic veins. A pedicle was formed and the tumor removed. Several hours after operation the patient died.

The salient features of the autopsy were as follows:

The patient was an obese young woman. There was no jaundice and no telangiectases or angiomatous nodules in the skin or mucous membranes. The peritoneal cavity was free of fluid and adhesions. The liver was large and weighed 2,300 gm. The entire surface, especially that of the right lobe, showed numerous small deep blue areas somewhat depressed below the surface. They

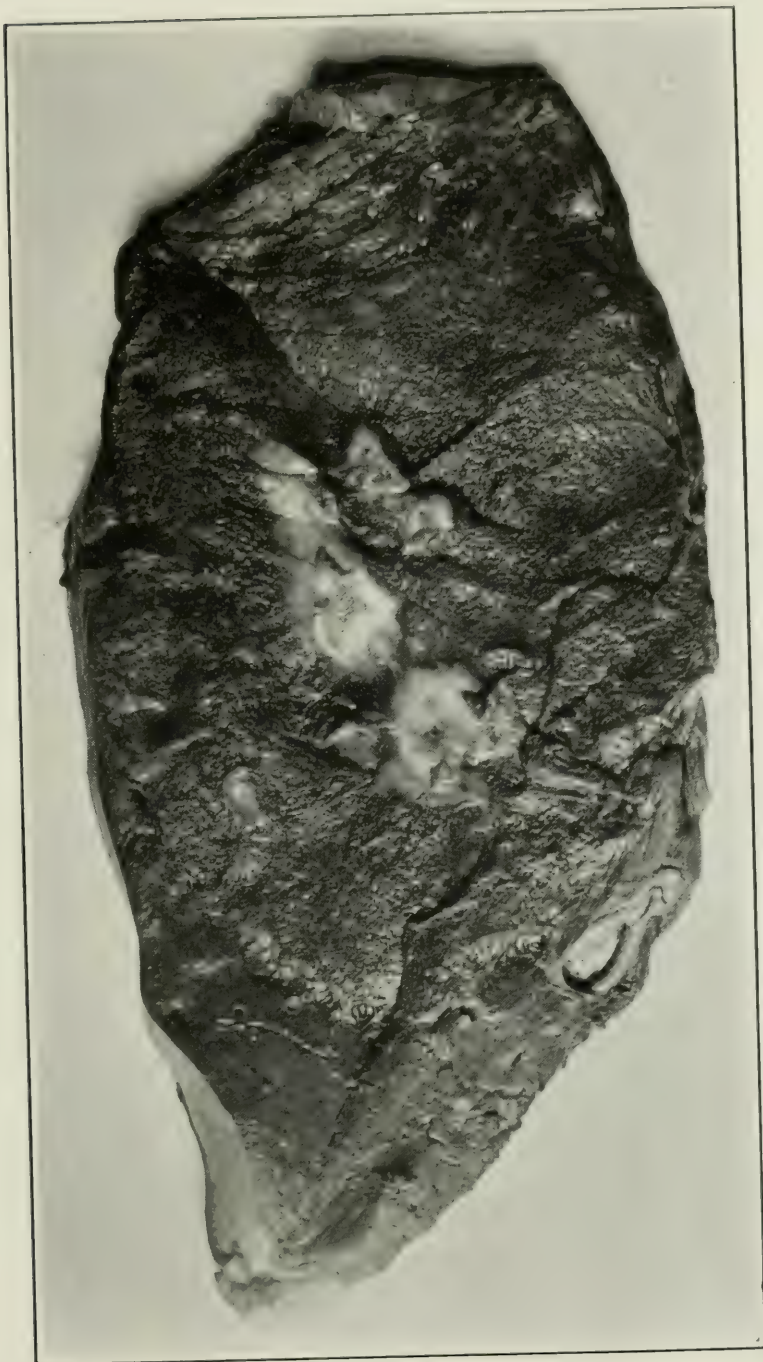


FIG. 1. Shows large tumor mass in liver with areas of fibrosis in the center

measured between 2 mm. and 2 cm. in diameter. On cut section, they were deep red in color, contained a great deal of blood and had a spongy appearance. On close inspection it was found that they were traversed by very fine grayish fibrous strands with spaces containing blood which gave the lesion its sponge-like character. On incising the liver there were found several large and small deep red areas which appeared to be fairly well demarcated from the liver parenchyma and which contained a great deal of blood. These areas measured from 2 cm. to as large as 15 cm. in diameter. In the center of many of the larger areas were other areas of light yellow fibrous tissue which sent strands out into the tumor mass. The portions of the tumor masses which were reddish had a sponge-like appearance, being made up of minute cavities containing blood which were separated from one another by fine fibrous strands of connective tissue. There was an extra branch of the hepatic vein which ran from the lower margin of the right lobe to the inferior vena cava and which was probably in close relation to the tumor removed at operation.

The microscopic examination of the tumor excised showed a typical cavernous hemangioma. The blood spaces were lined by a single layer of endothelium. The tumor masses were well circumscribed from the surrounding liver by connective tissue. No communication between the portal or hepatic veins and the blood spaces could be demonstrated. The yellowish firm area consisted of masses of connective tissue. In some of the blood spaces thrombosis and organization had taken place. The smaller tumor masses consisted of wide blood spaces lined by endothelium separated from one another by strands of fibrous tissue. There was no definite indication that the blood spaces were in direct communication with either the portal or hepatic vein. The surrounding liver tissue appeared to be normal. The bile ducts were also negative. There were no areas of hemorrhage except at the site of removal of the tumor mass. There was no evidence of new growth.

The significance of the anomalous hepatic vein in this case is difficult to determine. Its close relation to the tumor mass removed would lead one to suspect that it might in some way be connected with the growth. Roggenbein published several cases of communication between the blood spaces and branches of the hepatic vein. This we have been unable to demonstrate in our case in any of the various sections examined. Nor is there any evidence of new growth in any of the sections. Of course, there is always the possibility that many of the tumor areas increased in size by a single process of hypertrophy. One would be more inclined to accept the theory advanced by Schmieden that the condition is probably one of malformation or error of development with subsequent hypertrophy.

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GANGLIONEUROMA OF THE MEDIASTINUM

LEO EDELMAN, M.D.

(From the Pathological Laboratory, Mount Sinai Hospital, New York)

I am presenting this specimen with a brief report of the history because of the relative infrequency of a ganglioneuroma oc-

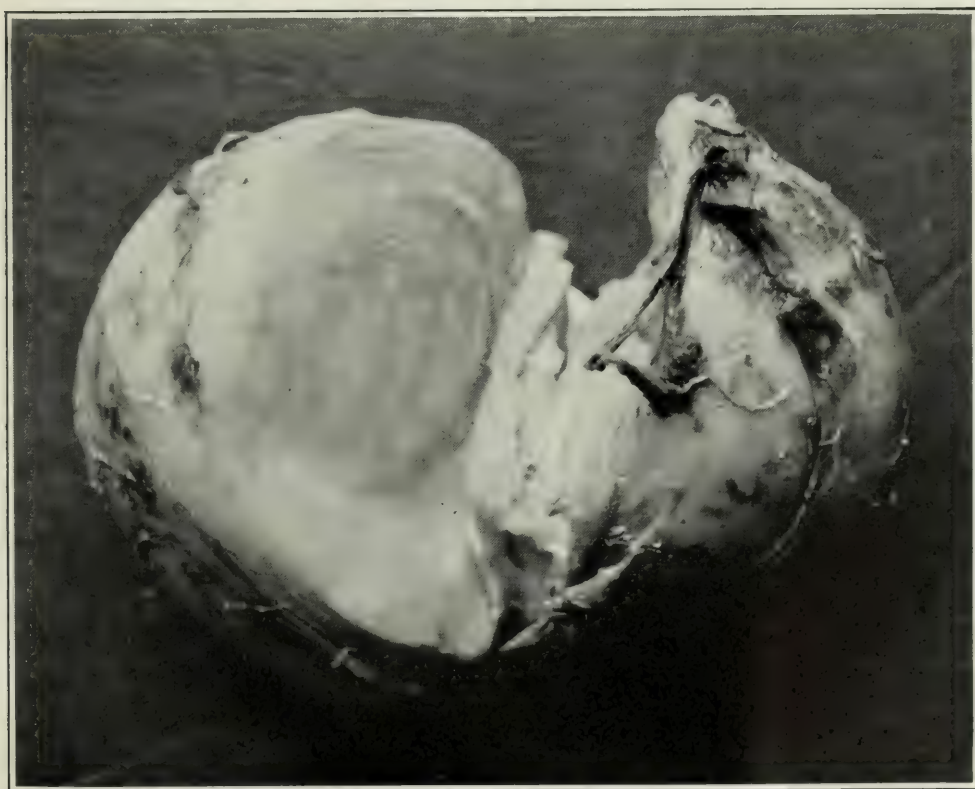


FIG. 1. Photograph of specimen split to show capsule and cut surface

curing in the mediastinum, together with the fact that the tumor was successfully removed at operation.

The specimen was removed from a girl, aged eight, admitted to the Pediatric Service of Dr. Henry Heiman, January, 1922, complaining of a persistent cough associated with intervals of moderate irregular fever, progressive weakness and loss of weight, all of which had existed for about seven months. She was a full term child and the family history was negative.

On physical examination, the patient appeared markedly undernourished, weighing only forty pounds, pale, with a short hacking cough. She presented physical signs indicating the presence of some pathological condition in the upper right chest. The x-ray plate suggested the presence of an encapsulated effusion which occupied the region of the right upper lobe extending to the third rib anteriorly, and an unresolved pneumonia at the right base. The blood showed a moderate leucocytosis. The Von Pirquet test was negative. Re-

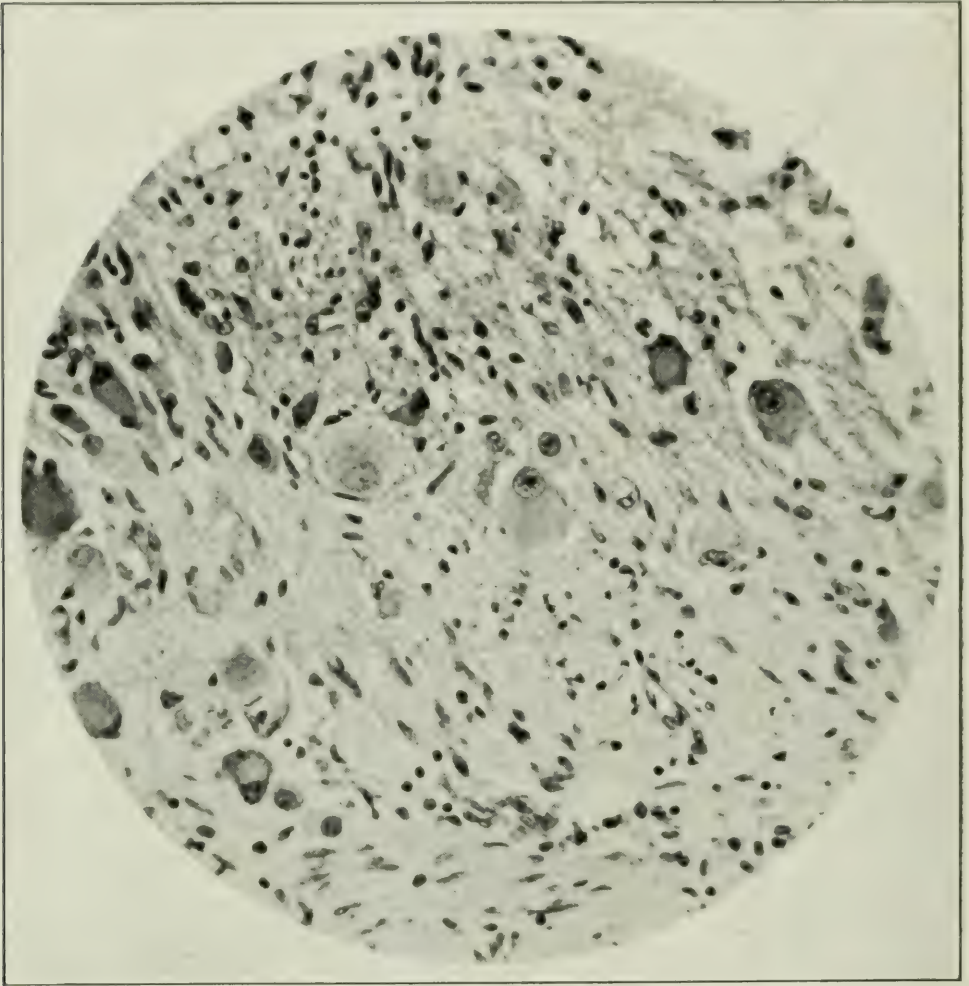


FIG. 2. Microphotograph, high magnification, showing ganglion cells

peated aspirations of the chest failed to locate pus. Owing to the continued decline in the child's condition, she was transferred to the service of Dr. Howard Lilienthal for surgical intervention. On February 14, 1922, he removed the tumor. The patient made an uneventful recovery and was subsequently presented before the Pediatric Section of the Academy of Medicine in May, 1922, by Dr. William Rosenson. At operation the tumor was found to be encapsulated, the size of a tennis ball, springing from the right upper mediastinal region. It was fixed only to the mesial side and above to the fascia covering the spine, from which it was easily separated.

The specimen when received in the laboratory in the fresh state measured 8.5 x 6.75 x 4.5 cm. and weighed 154 gm. It was pale yellow in color, rather spherical in shape, firm, and completely encapsulated by a thin fibrous membrane. The capsule could be stripped off easily. On section (Fig. 1), the cut surface presented a uniform pale yellow glistening appearance, roughly divided into nodules by fibrous septa suggestive of an edematous fibroma or sarcoma. Small hemorrhagic foci were scattered throughout.

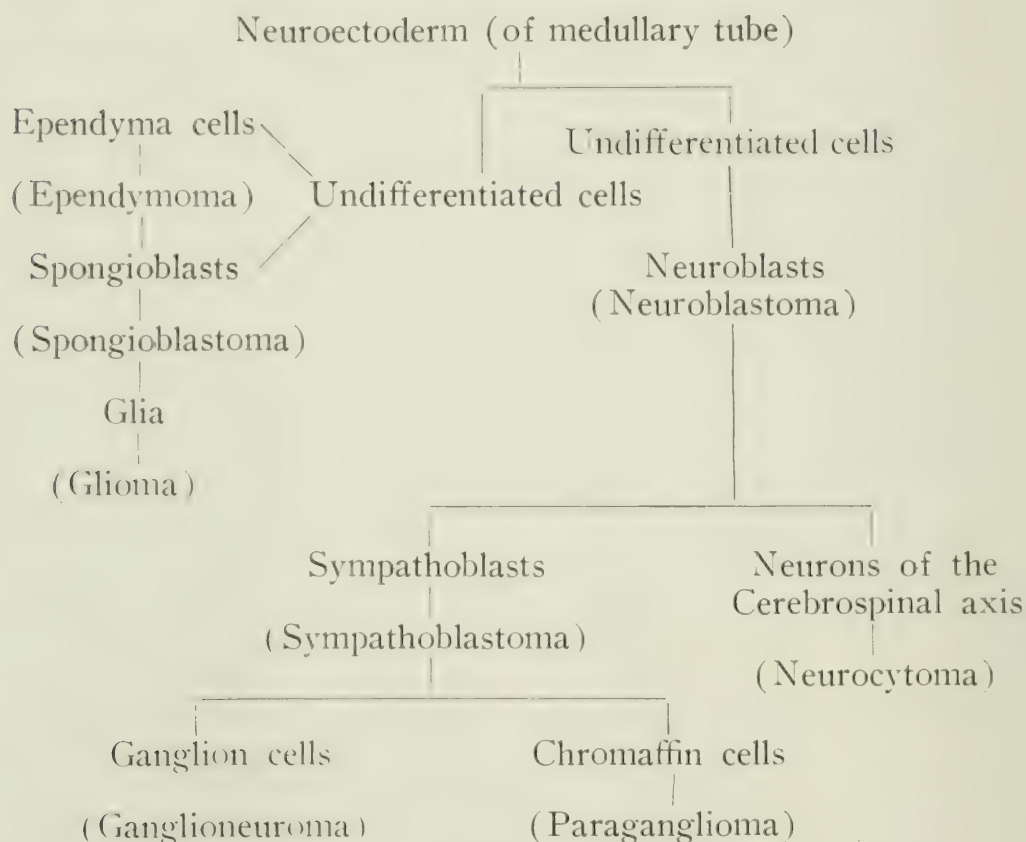
Under the microscope sections taken from various parts of the tumor present numerous ganglion cells showing characteristic proliferative and degenerative changes, and nerve fibrils, some of which are arranged in parallel bundles suggesting embryonic nerves, supported by fine connective tissue fibers and blood vessels (Fig. 2). The proportions of these elements present varied markedly in different parts of the slide and in the different sections. There is also some evidence of hemorrhage and round cell infiltration.

The description of the tumor in the gross and the microscopic picture as recorded above correspond to the characteristic appearance of similar cases reported in the literature. The diagnosis was made by Dr. F. S. Mandlebaum, to whom I am indebted for the privilege of making this presentation.

The term "ganglioneuroma" has been applied to a tumor originating almost exclusively from ganglion cells and nerve fibers of the sympathetic nervous system. It may occur at any age, but more commonly affects children and young adults and is rather rare after the third decade. The adrenal is the most frequent site for its growth. It occurs less commonly in the retroperitoneum or mediastinum, but owing to the wide distribution of sympathetic nervous tissue, it may arise almost anywhere in the body. Dunn¹ in his review of fifty-one reported cases found five arising from the thoracic segment. Stout² added another case occurring in a child two and a half years of age in which the tumor occupied the upper left thoracic cavity, arising from the upper thoracic vertebræ. The present case is the seventh to be recorded in the literature. The size of the tumors observed varied from that of a cherry to that of a man's fist and according to Falk³ bears an inverse ratio to the age of the individual. He also concludes that the younger the patient the more undifferentiated and malignant is the growth apt to prove, malignancy being due to the fact that it is of a mixed type. Wahl⁴ described a remarkable case in a child two and a half years of age, in which all three of the

well-recognized tumors originating from sympathetic nervous tissues were present, namely, malignant neuroblastoma, ganglioneuroma, and paraganglioma.

Several excellent reviews on the subject of tumors of the sympathetic nervous system have appeared which shed considerable light on the histogenesis of ganglioneuroma, notably Falk,³ Wegelein,⁵ Wahl,⁴ and Lambert.⁶ They are all of the same opinion, that one must assume an embryonal disturbance of the structure of the sympathetic nervous tissue with the presence of superfluous undifferentiated tissue in the region giving origin to the tumor. The following diagram, taken from the paper by Strauss and Globus,⁷ illustrates in a simple and concise way the relationship of this tumor to other tumors neuroectodermal in origin.



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Discussion:

DR. MACNEAL: This is a very rare type of tumor. I can recall only one ganglioneuroma* which has come on our service during twelve years, and that, curiously enough, does not lend itself to the classification which has been presented here. This example was a fusiform swelling of the optic nerve, perhaps 15 or 20 cm. in length, with a diameter of possibly 8 or 9 mm. The cut surface appeared very much like this, and showed the same homogeneous yellow appearance. The fusiform swelling seemed to occupy the entire sheath of the optic nerve, and was thought to have developed from the optic nerve structure. The possibility remains that it might have developed from sympathetic innervation about the central vessels of the optic nerve. These things are so rare that one hesitates to interpret such a specimen.

I should like to ask Dr. Edelman whether there was any evident connection with the sympathetic nervous system in his specimen.

DR. EDELMAN: There was a small pedicle which was easily separated from the fascia covering the spine.

DR. MACNEAL: The connection with the sympathetic was not ascertained?

DR. EDELMAN: No, sir, it was not definitely ascertained.

SPECIMENS ILLUSTRATING VARIOUS TYPES OF PULMONARY SUPPURATION

P. W. ASCHNER, M.D.

The classification of suppurative diseases of the lungs due to non-specific forms of infection has been in a rather confused state. The subject has been dealt with chiefly in clinical works, and the microscopic appearances have been given but little detailed study. The specimens to be presented this evening are examples chosen from thirty-six cases operated upon by Dr. Howard Lilienthal in which one or more lobes of the lung were resected. I believe there is an advantage in having operative

*This tumor has been reported by Dr. Martin Cohen: A primary intradural tumor of the orbital portion of the optic nerve. *Arch. Ophthalm.*, 1919, xlviii, 19.

material for study. Autopsy material comes either from acute fulminating cases or from cases dying after a very prolonged illness in which the primary type of lesion has been masked by numerous secondary pathological processes.

In a previous paper (*Ann. Surg.*, 1922, lxxv, 321), the following classification was suggested:

1. Bronchiectasis
2. Bronchiectatic abscess
3. Suppurative pneumonitis
4. Extrabronchial abscess.

The portals of infection are naturally four: 1. Through the air passages. 2. Through the blood stream (embolic lesions). 3. By extension from neighboring structures, *e.g.*, the esophagus. 4. By traumatic introduction through the thoracic parietes. The suppuration may occur in a previously healthy lung, or in a lung which is the site of some preceding disease. For example, pneumonia or influenza, or an aseptic infarct of the lung may terminate in suppuration when pyogenic microorganisms are introduced.

BRONCHIECTASIS

By this is meant a more or less uniform dilatation of the bronchi and bronchioles. The process may be confined to one or two lobes, or may involve both lungs diffusely.

The first specimen is the left lower lobe of a girl sixteen years old, who was well until her fifteenth year when she had pain in the left chest and began to expectorate mucoid greenish sputum, increasing in quantity, with periods of febrile reaction. She was operated upon about one year after the onset of symptoms. The diseased lobe is smaller than normal, dark blue or purplish in color, and has a fine nodular or shotty feel due to the dilated terminal bronchioles. The line of resection shows ten or twelve bronchial branches, from one to two cm. in diameter, with dense thickened walls, redundant mucosa and purulent content. On longitudinal section the dilated air passages occupy most of the picture, the parenchyma being atelectatic.

The second specimen is the left lower lobe of a girl eighteen years old who had cough and foul expectoration for nine years. It shows practically the same appearance as the first one, but there are larger terminal sacculations.

The third specimen is the left lower lobe of a boy aged six years who had a respiratory infection diagnosed as pneumonia when he was three years old.

This was followed by cough and purulent expectoration which persisted. In this instance the parenchyma shows more inflammatory involvement.

The fourth specimen is the right lower lobe of a girl four and a half years old who was admitted to the hospital soon after the aspiration of a nut. Coughing, cyanosis, and fever developed, and by bronchoscopy the foreign body was removed, but suppuration developed and the diseased lobe was removed. The child succumbed, however, and at the autopsy another piece of nut was found occluding the eparterial bronchus and producing a similar pathology in the right upper lobe.

The microscopic sections show the tremendously thickened infiltrated mucous membrane of the bronchi thrown up into numerous rugæ. The enormous secreting surface explains the profuse expectoration which may occur in these cases. The elastic laminæ are either entirely absent or broken up by the inflammatory tissue. The parenchyma may show partial atelectasis, or varying degrees of acute and chronic pneumonitis. In more advanced cases the sacculations become ulcerated and abscesses form in the periphery of the lung.

The etiology of many of these cases is not clear. The mechanical factors may be primary in some. Thus, the youth of the patients suggests a possible congenital dilatation. Foreign bodies or tumors may obstruct the lumen. Compression by a mediastinal dermoid was the causative factor in another. The infection of the bronchial wall seems to be the primary element in others, as in cases following influenza, pertussis, or pneumonia. In a few cases disease of the paranasal sinuses seems to have an etiological rôle.

BRONCHIECTATIC ABSCESS

By this is meant a distinct type of pulmonary suppuration, namely, a localized abscess occurring in the course of a bronchus usually of the second order. The bronchus leads into an irregularly shaped cavity containing pus and necrotic material. From the walls of this cavity smaller bronchial radicles lead out into the lung. The other bronchi of the lobe are secondarily affected either by spilling over of pus into them or by compression or displacement resulting from the primary lesion with its surrounding area of indurated pneumonitis.

In my previous paper there were ten cases of this kind, all of which followed removal of the tonsils and adenoids under general anesthesia.

I present two specimens of this type. One is the right upper lobe removed nine months after tonsillectomy in a girl eight and a half years old. The second is the right lobe of a girl fourteen years old who had her tonsils removed six months previously. The cases of this type all present a similar clinical history characterized by an interval of twelve to fourteen days between the operation and the development of the purulent expectoration. There has been considerable difference of opinion as to the etiology, some believing that it is the result of aspirating tissue or infected blood at the time of operation, others claiming that it is embolic in origin from infected thrombi in the regional venules.

The microscopic sections of these specimens show several interesting findings. The wall of the abscess cavity is found to be lined by a stratified flattened epithelium beneath which the infiltrated submucosa and muscularis are seen if the section is made near the entering bronchus. More peripheral areas show a similar epithelial lining covering vascular granulation tissue (Fig. 1). In some cases the section taken in an area remote from the entering bronchus and near the periphery of the lung shows a very thin squamous epithelial lining.

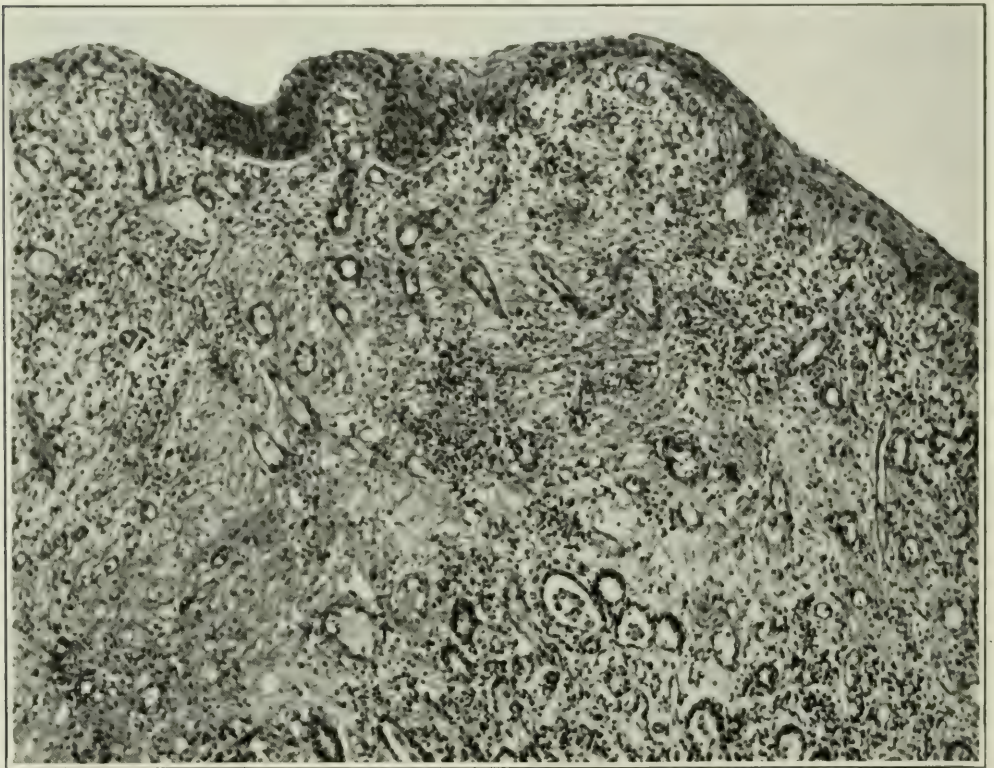


FIG. 1. Section through wall of bronchiectatic abscess, showing epithelial lining.

We can only account for this picture by the theory of aspiration as the cause of the disease. Infected tissue or blood clot is aspirated and occludes a bronchial branch. The secretions ac-

accumulate behind the obstruction and cause a localized dilatation in which the element of infection plays an important part. After a varying interval the abscess thus formed is evacuated through the bronchus. The lining epithelium of the cavity undergoes metaplasia with pavement cells replacing the normal columnar cells. In parts of the wall of the cavity granulation tissue or dense fibrous tissue is found. Haythorn (*Jour. Med. Research*, 1912, xxvi, 523) has also described metaplasia of the bronchial epithelium.

Another histological picture of interest is found in some specimens. Islands of ductlike structures lined by low cuboidal epithelium are seen in areas of dense fibrosis and remind us of the proliferation of the bile passages described by MacCallum in portal cirrhosis (Fig. 2). In one case this was so marked that the question of early malignancy was debated.

The two specimens now to be presented are of considerable importance. Dr. Wessler observed in his clinical studies of lung suppuration (*Jour. Am. Med. Assn.*, 1919, lxxiii, 1918) that the history of a considerable number of supposed post-pneumonic abscesses corresponded closely with that observed in the post-tonsillectomy group just described. These two specimens offer confirmatory evidence of his theory that this type of disease is also the result of aspiration infection.

The first is the right lower lobe of a man aged thirty-six years who was operated upon for acute gangrenous appendicitis under general anesthesia. He developed the typical symptoms and signs of a right lobar pneumonia from which he appeared to recover completely. He was discharged "well" twenty days after admission. A week later he returned to the hospital with the symptoms and signs of suppuration in the right lower lobe. Under expectant treatment he again seemed to get well but a relapse occurred and the diseased lobe was resected seven months after his appendectomy. The specimen presents the typical gross and microscopic characteristics of bronchiectatic abscess.

The second specimen is the right upper and middle lobes of a man thirty-one years old who developed cough and purulent expectoration following gastroenterostomy. He had been suspected of pulmonary tuberculosis, but no clinical or radiographic confirmation was obtained. Subsequent study revealed an abscess of the right upper lobe. This was resected together with the inseparable but healthy middle lobe. The specimen presents a large bronchiectatic abscess of the upper lobe, irregular in contour, with the usual microscopic features. In the parenchyma of the upper lobe the sections show small areas

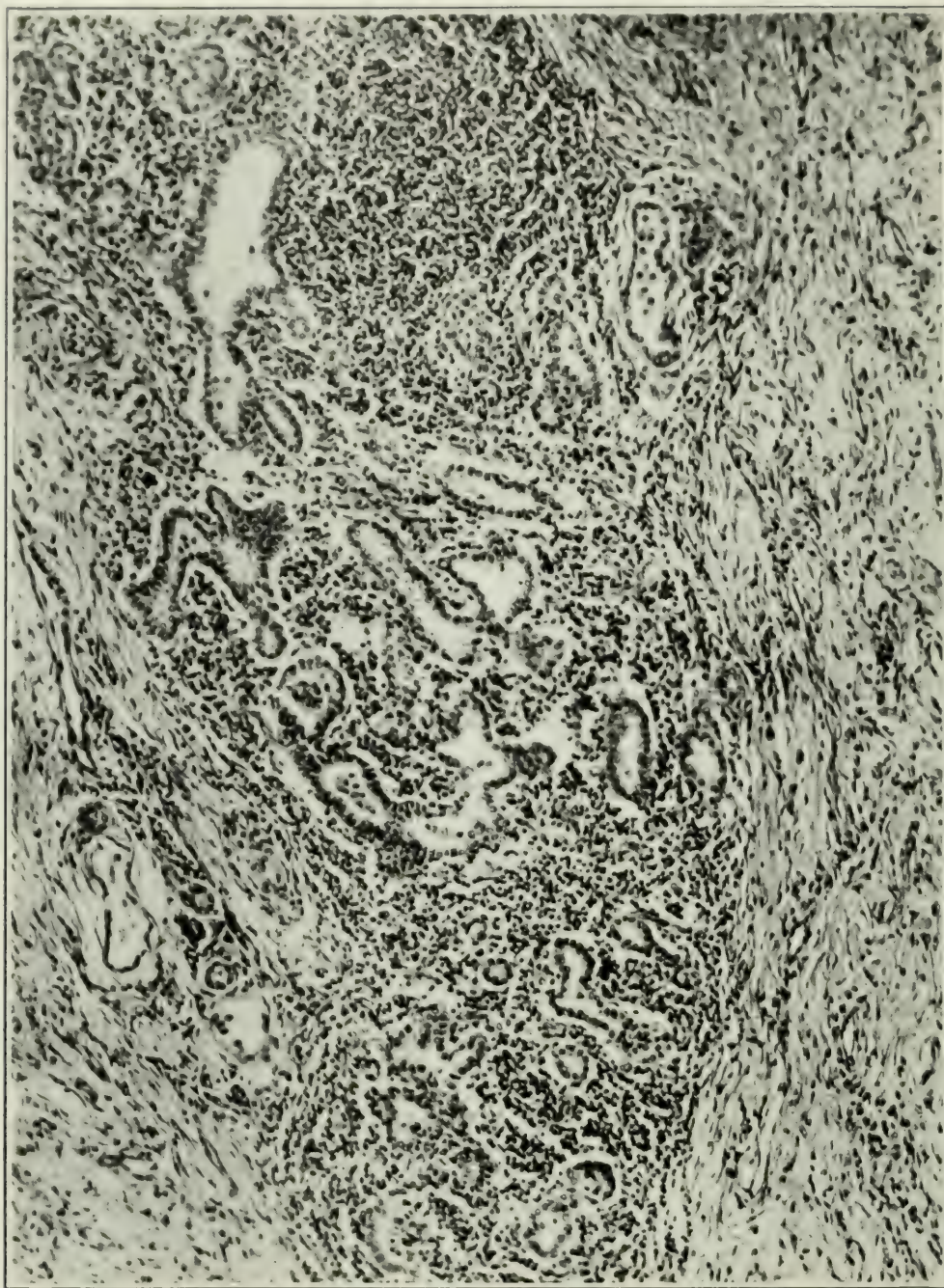


FIG. 2. Proliferation of air passages in an area of fibrosis.

of early tuberculosis. The abscess wall shows no evidence of tubercle. The middle lobe parenchyma is normal.

SUPPURATIVE PNEUMONITIS AND EXTRA-BRONCHIAL ABSCESS

These two forms of lung suppuration are not sharply delimited, and present a varied pathological picture. Suppurative pneumonitis is a rather diffuse process involving one or more lobes and is the result of a widespread infection entering by way of the air passages. The process may resolve for the most part leaving abscesses of the parenchyma which are extra-bronchial. The latter tend to rupture into the bronchial system or into the pleural cavity. This type of suppuration frequently occurs as a sequela of influenza.

The specimens which I now present are from the case of a girl eight years old whose tonsils were removed under general anesthesia three weeks prior to her admission to the hospital. She presented signs and x-ray findings of a pneumonic infiltration of the right lower lobe. Under observation the process was found to be spreading, and although her condition was very grave, operation was undertaken. Both lobes of the left lung were found extensively diseased and were removed. She succumbed to a septic diarrhea and secondary hemorrhage from the stumps thirteen days later.

Both lobes show a diffuse spreading purulent pneumonitis, pus exuding from the bronchial branches and the parenchyma being studded with miliary abscesses. This specimen does not resemble the ordinary post-tonsillectomy cases in any way and on consulting the clinical history it was found that the symptoms began in an acute form a few days after the operation. The pathological findings and the history resemble more those cases of suppuration following submersion. A large amount of infectious fluid material must have been aspirated.

Discussion:

DR. SCHWARZ: I should like to ask one question. Is that squamous epithelial lining a regular feature of bronchiectasis?

DR. ASCHNER: In all the post-tonsillectomy cases sections of various areas in the abscess wall were taken. In 90 per cent. of these cases we were able to demonstrate, at least in some parts of the wall, this squamous epithelial lining. It is perfectly true that you will find areas where it is not present, and where there is destruction of the lining epithelium. In the bronchiectasis cases we found metaplasia in some of the terminal sacculations.

DR. SCHWARZ: In common pus sacs the metaplasia into squamous epithelium is a rather common occurrence. I have noted the coexistence of leukoplakia of the uterus with pyometra. It seems to me that pus has that particular influ-

ence on columnar epithelium; sometimes small or larger areas of squamous epithelium develop in these cases. We can not very well assume that there is any squamous epithelium creeping in from the neighboring mucosa, because it is rather high up, so metaplasia is actually the only explanation.

SYPHILITIC ATHEROSCLEROSIS OF THE PULMONARY ARTERY PRESENTING CLINICALLY THE SYMPTOMS OF AYERZA'S DISEASE

FREDERIC D. ZEMAN, M.D.

(From the Pathological Laboratory, Mt. Sinai Hospital, New York City)

The case which I wish to present illustrates an interesting pathological process in correlation with an unusual clinical picture. Professor Warthin was the first to report a case of this type in this country, and, as far as I have been able to discover, his case is still unique in the American literature.

The patient, L. B. S., first came under medical observation at Lebanon Hospital six years ago, at the age of fifty-three. At this time he gave a history of pulmonary tuberculosis five years before, which had become quiescent. For five months prior to his admission to Lebanon Hospital he had suffered from dyspnea on exertion and swelling of the abdomen. On examination he was found to be extremely dyspneic even while at rest. Intense cyanosis of the face, body, and mucous membranes was observed. Cardiac enlargement, both to the right and left, was noted, in conjunction with weak heart sounds. The lungs showed an infiltration at the right apex, and a generalized bronchitis. Although the abdomen was distended, no signs of fluid were made out. The liver and spleen were not felt.

The Wassermann reaction was positive. The sputum contained tubercle bacilli. Roentgen examination of the chest showed diffuse widening of the aortic shadow, and a definite involvement of the right apex. The blood count revealed hemoglobin, 135 per cent.; red cells, 8,000,000; white cells, 12,000, of which 83 per cent. were polynuclears. After a month's stay in the hospital the patient was discharged improved with a diagnosis of chronic pulmonary tuberculosis and syphilis. The significance of the polycythemia and cyanosis was at this time not clearly recognized.

During the following six years the patient was troubled by cough, occasional hemoptyses, and symptoms of cardiac insufficiency. His cyanosis persisted with varying intensity, and swelling of the legs recurred from time to time.

On January 10, 1923, he was admitted to Mt. Sinai Hospital in an extremely critical condition. The abdomen and legs had been swollen for three months; dyspnea, cyanosis, and cough had increased steadily. On examination

he was found to be intensely cyanosed, orthopneic, and with extensive anasarca. Chest examination showed a large heart, with weak sounds but no murmurs, together with signs of emphysema and pulmonary congestion. The liver was enlarged but not pulsating. The spleen was not palpated. Ascites was very marked, with edema and cyanosis of the extremities. The blood pressure was systolic, 112; diastolic, 88. The hemoglobin was 130 per cent.; white cells, 14,000, of which 78 per cent. were polynuclears. The Wassermann reaction was positive. In spite of stimulation, the patient's condition grew steadily worse, and he died twenty-four hours after admission.

Clinically, this patient presented a most intense cyanosis, and dyspnea of at least six years' duration, associated with evidence of pulmonary disease, a well-marked polycythemia, as well as clinical and serological evidences of syphilis.

At autopsy, there was found a very striking dilatation and hypertrophy of the right auricle and ventricle, with a relative tricuspid insufficiency. The pulmonary valve was slightly thickened but apparently competent. The left ventricle and auricle showed some dilatation and hypertrophy. The mitral orifice admitted three fingers with ease. The heart muscle was brown, flabby, and on section showed a few gray linear scars. The coronary arteries presented a diffuse atheromatous change.

The arch of the aorta was diffusely dilated; its elasticity was greatly diminished, and there was an advanced degree of sclerosis in the form of atheromatous plaques, ulcerated and calcified. There were also numerous areas most marked in the region of the arch and ascending portions, characterized by pearly plaques, longitudinal wrinkling, and scarring of the intima.

The main trunk of the pulmonary artery was greatly dilated and presented definite thickening of its wall with great loss of elasticity. The intima was studded with areas of atheromatous change. At one point near its division into the two main branches, there was definite wrinkling and scarring. Marked atherosclerotic changes were observed in even the smallest ramifications of the artery throughout the lungs.

The lungs were bound down to the parietal pleura by many firm fibrinous adhesions. At the apex of each lung was found an area about the size of a walnut consisting of partially calcified fibro-caseous tissue. The lung parenchyma was generally emphysematous, congested, and edematous. In the lower lobes a few small areas of broncho-pneumonia were noted.

The peritoneal cavity contained about six liters of straw-colored fluid. The gastrointestinal tract showed marked chronic passive congestion, as did also the kidneys.

The liver weighed 1,350 gm. Its consistency was unusually firm, and its surface presented a granular irregularity. On section, the parenchyma was extremely congested with a nutmeg appearance. The gall bladder was shrunken, its wall fibrosed and it contained a single large green calculus. The bile ducts and portal vein were negative.

The spleen was not enlarged, weighing 130 gm. The capsule was slightly wrinkled, but the consistency of the organ was firm and elastic. On section the pulp was congested and the Malpighian follicles were made out with some difficulty.

Microscopically, the aorta showed marked hyaline thickening of the intima, diffuse scarring of the media with perivascular infiltration of the vasa vasorum in the adventitia and media, by round cells and plasma cells. The pulmonary artery in the main trunk and larger branches showed changes similar to those observed in the aorta but of less intensity. The intima showed atheromatous changes, and definite perivascular infiltrations in the adventitia, less marked in the media. In the smaller vessels in the lungs the purely atherosclerotic changes predominated, with marked narrowing of the lumen in some places, in other places dilatation. Occasionally, smaller vessels were encountered which gave evidence of a more active inflammatory process by a cellular infiltration of the media by plasma cells and round cells. The heart muscle showed marked edema, occasional small fibrous scars and atrophy of muscle fibers, with a few small areas of round cell infiltration beneath the pericardium. Histologically, the spleen showed congestion, dilatation of the sinuses, and thickening of the reticulum. The vessels presented an advanced degree of atheromatous change. The lungs showed purulent bronchitis and peribronchitis with emphysema and congestion. In the lower lobes a few small areas of bronchopneumonia were observed. The kidneys showed areas of focal nephrosclerosis. The liver presented marked congestion with atrophy of the cells at the center of the lobules, and numerous areas of fibrosis with new-formed bile ducts, and infiltration by round cells and fibroblasts. The adrenals showed an unusual degree of fibrosis of the cortex with infiltration by round cells. Special stains for spirochetes are now being carried through, but at the present time it is impossible to report on this important point.

The pathological conditions found at autopsy were as follows: general atherosclerosis; syphilis of the aorta and of the pulmonary artery; relative tricuspid and mitral insufficiency; marked dilatation and hypertrophy of the right auricle and ventricle; myocardial degeneration; chronic passive congestion of the lungs and abdominal viscera; chronic cholecystitis and cholelithiasis; chronic adhesive pleurisy; bilateral pulmonary tuberculosis (healed); ascites; terminal acute bronchopneumonia; acute purulent bronchitis and peribronchitis.

The association of pulmonary atherosclerosis with polycythemia was first pointed out by Ayerza, a clinician of Buenos Ayres, who in 1901, in a clinical lecture, described a symptom complex which he termed *cardiacos nigros* or black cardiacs. The characteristic symptoms in these cases were cyanosis, polycythemia, cough with purulent or mucopurulent sputum, headache, vertigo, and hemoptysis. This clinical concept has been enlarged and further developed by several of Ayerza's pupils, the most notable of whom is Arillaga.¹ His monograph covering eleven cases appeared in 1913, and described the clinical course and pathology in detail. He emphasized the gradual onset of the symptoms following some pulmonary condition, long

before the appearance of symptoms of cardiac insufficiency, a point which serves clinically to differentiate this type of cyanosis from that occurring in acute cardiac decompensation. He found the regular pathological change in these patients was a well-defined atherosclerosis of the pulmonary arteries, associated with a dilatation or hypertrophy of the right heart. These lesions in the pulmonary vessels he attributed to a combination of factors, but chiefly to conditions which tend to raise the blood pressure in the pulmonary circuit, such as mitral stenosis, bronchitis, pleural adhesions, emphysema, or tuberculosis. Syphilis, malaria, or chronic intoxications may be important predisposing influences. Splenomegaly is by no means a constant finding.

The case reported here is strikingly similar to the one described by Warthin² in 1919, which up to the present is the only case of its kind recorded in this country. His paper is particularly valuable for its review of the South American sources. His patient showed all the cardinal symptoms and signs of the disease as described above, and gave evidence of syphilis both clinically and pathologically. Warthin emphasizes particularly the secondary character of the polycythemia. The bone marrow in his case showed a definite erythroblastic hyperplasia.

An important distinction must be drawn between this condition and the true or primary polycythemia of Vaquez and Osler. F. Parkes Weber,³ in a recent monograph on polycythemia, discusses Ayerza's disease in detail and includes it in the group of the secondary polycythemias. He prefers the name "erythrocytosis of cardiopulmonary origin" for this syndrome. This author also lays stress on the fact that syphilis is by no means a necessary or frequent etiological agent.

The occurrence of syphilitic lesions in the pulmonary artery is relatively rare if one may judge by the paucity of the literature on the subject, and the fact that most text books fail to mention it. In 1917⁴ Warthin collected 75 cases and reported one of his own in which he was able to demonstrate the *Treponema pallidum* in the wall of the vessel. In discussing the various forms in which syphilis may affect the pulmonary vessels, he differentiates the

following: (1) diffuse pulmonary atherosclerosis, (2) gummatous arteritis, (3) solitary gumma of the arterial wall, (4) aneurysms. The histological picture is similar to that observed in luetic aortitis and represents a specific pathological alteration which fully justifies a microscopic diagnosis of syphilis.

Simple atherosclerosis of the pulmonary arteries occurs frequently in mitral stenosis, asthma, chronic bronchitis, emphysema, extensive pleural adhesions, and fibroid phthisis. In our case the emphysema is very slight, in fact, quite insufficient in itself to account for the extreme degree of atherosclerosis observed. Nor can the small foci of healed tuberculosis in the apices be held responsible for the very marked vascular changes. In view of the gross and microscopic evidences of syphilitic arteritis in the main pulmonary vessels, there is reason to consider syphilis as one of the main underlying factors which contributed to the development of an extreme atherosclerosis of the pulmonary vessels. A similar association is seen in the aorta where luetic aortitis is almost regularly associated with more or less marked atheromatous changes of a non-specific character.

These changes in the pulmonary vessels, extending into the smallest branches, produced a real obstruction to the blood flow through the lungs. This is attested to by the marked dilatation and hypertrophy of the right auricle and ventricle. As a result of these changes, the respiratory interchange was interfered with, and the bone marrow responded with an increased production of red blood cells such as is observed quite regularly in conditions causing a chronic oxygen deficiency. The polycythemia in this case reached an unusually high figure, such as is usually seen only in true primary erythremia.

In view of the very variable underlying pathology it is questionable whether the syndrome described by Ayerza should bear his name as a distinct clinical entity. Mild degrees of polycythemia certainly occur too frequently in connection with emphysema, asthma, and bronchitis to deserve a special nomenclature. The view expressed by Parkes Weber would seem to be a very rational one, and until many of the details of the pathogenesis of

this condition are cleared up, it seems best to refer to this condition, as he suggests, as "erythrocytosis of cardiopulmonary origin."

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DR. LIBMAN: I do not believe that the studies of Ayerza were known in this country or in Germany until Dr. Warthin presented his report on the subject at the meeting of the Association of American Physicians. In 1904 Neubauer reported from the clinic of Professor Von Mueller a very remarkable case which was considered clinically to be a case of congenital heart disease on account of the cyanosis, and which proved to be a case of diffuse atherosclerosis of the pulmonary artery and its branches. This was one of the first cases which drew attention to the connection between cyanosis and disease of the pulmonary artery. It is interesting to note that in cases of transposition one may find cyanosis without cardiac murmurs. In young people one might very well have to make, at times, a differential diagnosis between disease of the pulmonary arteries causing cyanosis and transposition.

I do not believe that it is a bad idea to use the name of "Ayerza's disease" for the present and to limit it to disease of the pulmonary artery with cyanosis, accompanied or not by an enlargement of the spleen. Dr. Zeman has pointed out that in the cases described by Ayerza the spleen was not always enlarged. The value of keeping the name is that when one sees a case of cyanosis, one would always think of examining the patient for a disease of the pulmonary artery.

As Dr. Zeman read the history of the case, I noted that a leucocytosis was not present. In erythremia we practically always find a leucocytosis. It would be interesting to go through the literature and find out whether the cases of "Ayerza's disease" had a leucocytosis or not. This point might be of value in differential diagnosis. Whether the leucocytosis in cases of erythremia lasts into an anerythremic stage, I do not know. In some cases of erythremia, in the later history of the disease, the hemoglobin and the number of erythrocytes may decrease to below the normal figure.

THE OCCURRENCE OF GLOMERULONEPHRITIS IN ASSOCIATION WITH VERRUCOUS ENDOCARDITIS *

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Since the criteria for the differentiation of the various types of endocarditis have been more clearly defined, it has been possible to obtain more accurate knowledge concerning the renal lesions occurring in each of these types. The most completely studied of the renal lesions are those occurring in subacute bacterial endocarditis. The focal embolic glomerular lesions described by Loehlein and extensively studied by one of us (G. B.)¹ are characteristic of the latter disease.† In this type of lesion, minute bacterial emboli cause injury to a limited number of loops of a variable number of glomeruli.

In the active cases, *i.e.*, when both the blood and the vegetations contain the characteristic organisms, the kidney lesions are found in all stages of development. In the cases described by Libman² as the bacteria-free group, *i.e.*, when the vegetations are healed and neither the blood nor the vegetations contain bacteria, only healed embolic glomerular lesions are found in the kidney. The finding of these lesions is of the greatest value for corroborating the post-mortem diagnosis of cases belonging to the bacteria-free group.

In addition to these focal lesions, diffuse glomerular damage also occurs in subacute bacterial endocarditis.³ It appears that certain of the individuals suffering from this disease develop acute diffuse glomerulonephritis during the active stage as the patient is becoming bacteria-free, and that as healing of the endocarditic

* Work done under tenure of George Blumenthal, Jr., and Leo S. Bing Fellowships in Pathology.

† The focal embolic glomerular lesions have recently been found in two cases where no endocarditis was present. In the one case, there was a generalized miliary actinomycosis, and in the other focal necroses in the liver of obscure origin and adherent pericardium. Thus far, these have been the only instances in which the lesions occurred in the absence of subacute bacterial endocarditis.

lesions continues, the acute process progresses into a chronic one. Clinically, it is found that a certain percentage of cases of subacute bacterial endocarditis in the bacteria-free stage develop the signs of renal insufficiency and die of uremia, and at autopsy the healed lesions are found on the heart valves and mural endocardium, and the kidneys show chronic diffuse glomerulonephritis.

In rheumatic endocarditis, the focal embolic lesions characteristic of subacute bacterial endocarditis do not occur. These lesions serve, therefore, as a most valuable criterion of differentiation between these two types of endocarditis. Acute diffuse glomerulonephritis is of rare occurrence in rheumatic fever. In the autopsy records of the Mount Sinai Hospital, there is not a single instance of acute or subacute glomerulonephritis in a case of rheumatic endocarditis with Aschoff bodies in the myocardium.

The Aschoff bodies are specific for rheumatic fever, and their presence is final proof of the rheumatic nature of a given valvular lesion. It must not be assumed, however, that cases of rheumatic endocarditis do not occur in which Aschoff nodules are absent from the myocardium. Clinically, there are cases which present the typical picture of rheumatic fever and which show at autopsy vegetations on the heart valves similar in morphology to the proven rheumatic form, but no Aschoff nodules in the myocardium. Many of such cases are undoubtedly instances of rheumatic infection, others are probably not; but in the absence of the knowledge of the specific agent of the disease, it is well for the purposes of differential study to leave open the question of the exact nosological position of all cases of verrucous endocarditis morphologically similar to the rheumatic form but without Aschoff bodies.

The kidneys were studied in seventy-five cases of verrucous endocarditis, including twenty-one showing Aschoff bodies in the myocardium. Acute or subacute diffuse glomerulonephritis was found five times in cases of verrucous endocarditis showing no Aschoff bodies in the myocardium. No instance was observed in a case where the Aschoff bodies were present. Two of the five cases definitely belong to the atypical form of verrucous endo-

carditis described by Libman and one of us (B. S.).⁴ It is not within the province of this paper to discuss these cases. The remaining three occurred in cases of verrucous endocarditis very similar to the proven rheumatic form. The peculiarity of these cases is that in addition to the usual changes found in acute diffuse glomerulonephritis, marked vascular lesions were found in the glomerular capillaries and arterioles of the kidneys and in one case in the small vessels of the heart.

At present we wish to present only a summary of the findings in the kidneys. At a later time, we shall publish a more detailed report in which the clinical histories and the individual autopsy findings of these cases will be given.

In addition to the glomerular changes generally found in acute diffuse glomerulonephritis, numerous thrombi were found in the glomerular loops, and the inflammatory process was found to extend into the arterioles, particularly the vasa afferentia. In the mildest form of involvement, the changes in the latter consisted of endothelial swelling and proliferation. In the more severely damaged arterioles, there was irregular hyaline degeneration and necrosis of the normal elements of the vessel wall, with karyorrhexis of many of the nuclei, infiltration at times with polynuclear and round cells, and the deposition of fibrin and blood platelet thrombi in the lumen. These changes were often limited to the vasa afferentia close to the pedicle of the glomerulus; in other instances they extended as far as the terminal segments of the interlobular arteries. Some of the arterioles showed thrombus deposition with comparatively little inflammatory change in the vessel wall. The variation in the degree of change in the arterioles in different parts of the same kidney was often striking.

Similar but less marked arteriolar changes were described by Loehlein⁵ in a group of cases of acute glomerulonephritis not associated with endocarditis. He calls attention to the fact that these changes are not seen in the earliest stages of the disease, appearing only in cases which have lasted at least several weeks. He finds the occurrence of slight changes in a large number of cases, but the severer changes only in 10 to 20 per cent. of the cases coming to post-mortem examination.

In a study of a series of cases of glomerulonephritis without endocarditis, we have observed the arteriolar changes several times, but in only one instance could they be regarded as approaching in intensity those found in the cases described above. The agent causing ordinary diffuse glomerulo-nephritis is therefore also peculiarly endotheliotropic. It seems to differ from the agent in our cases only in the fact that it seldom manifests such an extreme degree of endotheliotoxic potency.

There apparently exists a virus which, because of its affinity for endothelial structures, causes verrucous endocarditis, glomerulonephritis, and widespread arteriolar disease (kidneys, heart, and possibly elsewhere). Whether these cases constitute unusual forms of rheumatic fever, or whether they are related to the atypical group of endocarditis mentioned above, can not be definitely decided at present.

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Discussion:

DR. LIBMAN: In considering the incidence of diffuse glomerular nephritis in cases of subacute streptococcus endocarditis, Dr. Baehr and I found that this condition occurs at least fifteen times as frequently in cases which come under observation in what is called the bacteria-free stage as it does in cases which are encountered while bacteria are still present in the blood. Dr. Baehr, some years ago, made the suggestion that possibly the nephritis occurred at the time the bacteria were killed off. In Berlin, in some experimental work done on streptococci in mice, Kuczynski and Wolff came to a similar conclusion. In the case which I showed to-night, however, the glomerular nephritis occurred at the onset of the disease, so that in this particular instance the inflammatory process in the kidney could not be due to toxic action incidental to the killing off of bacteria. It is possible that in cases of subacute bacterial endocarditis, the idea may be correct.

DR. PLAUT: A paper was published about ten years ago on endocarditis in a journal which nobody has the custom to examine. In several cases of endocarditis the author took out pieces of the heart valves and made a very thorough series of sections. He cut them himself; nothing was done by a

technician, and he studied all of them for a long time. He always found very fine cocci, all of which he thought were of the type of *Streptococcus viridans*. I never have heard of his experience being repeated anywhere. He is a good observer, and he found these very fine cocci in the heart valves themselves. It would really be very fine if someone could repeat this very difficult and tedious experiment.

DR. LIBMAN: I am acquainted with the work of Reye and have referred to it in some of my papers. He usually found streptococci in very small numbers in the depths of vegetations in all kinds of verrucous endocarditis. Culturally, he found streptococci (of the type which he calls viridans, and which we call anhemolytic) in one hundred per cent. of his investigations. This theoretically is a most interesting point. From a practical standpoint, it does not mean much because of the frequent presence of anhemolytic streptococci in diseased organs. These studies give us no trouble in deciding whether a patient has a subacute streptococcus endocarditis or not, because in the latter disease, in the active stage, the surface of the lesion is one mass of bacteria.

Kinsella and Swift cultured anhemolytic streptococci from the blood in eight and three tenths per cent. of the cases of rheumatic fever which they investigated. They regarded them as secondary invaders because of the lack of an immune reaction. In studies made after death they found streptococci present in fifty per cent. of the cases. It is possible that what Reye found was evidence of secondary invasion, or he may have duplicated Rosenow's work. From the studies of the latter, we know that such organisms are ubiquitous.

DR. PLAUT: It is very interesting for me to hear what Dr. Libman says about the anhemolytic streptococcus, and it makes me think more and more of what I decided years ago. Here in America you get the anhemolytic streptococcus as a secondary invader, but we never find it in Hamburg. We were always looking for it, and we made bacteriological examinations of heart blood at every autopsy, but we never have found the anhemolytic streptococcus. We have read the papers of Rosenow, and we can not explain it, so that I think the anhemolytic streptococcus here is perhaps not the same thing as it is in Europe. I can not see another explanation of the differences between the results here and in Europe. It is not difficult to think that there are differences in the strains here and the strains to be found in Germany. Never, I must repeat it, have we found *Streptococcus anhemolyticus* as a secondary invader. Even in laboratories which have to do a great deal of bacteriological work only about once in two months may we find the streptococcus.

DR. LIBMAN: These observations of Dr. Plaut are very interesting. Last summer I met Professor Schottmueller, who is a splendid clinician and a valuable investigator. His mind, however, is rather rigid on the subject of anhemolytic streptococci. There was quite a discussion last year at the meeting of the German Congress for Internal Medicine, because one of the men actually said that you could find anhemolytic streptococci in the blood in patients other than those suffering from endocarditis. There is no question that that investigator was correct. In a paper which will soon appear in which I have dis-

cussed the whole subject of endocarditis, I have described eight conditions in which anhemolytic streptococci can be found in cultures made from the blood. I made the statement that we can get an antemortem invasion of anhemolytic streptococci in almost any disease, and even in cases of valvular disease. An interesting case in point was that of a patient who suffered from endocarditis originated by the influenza bacillus; from the blood of this patient anhemolytic streptococci were cultured a short time before the patient died.

DR. MACNEAL: Perhaps it might be said that not every American bacteriologist is able to obtain the streptococcus from various parts of the body with the same success as Dr. Rosenow has done. If Dr. Plaut has the impression that all American bacteriologists are so successful, it is an erroneous one.

ATYPICAL VERRUCOUS ENDOCARDITIS

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The specimen which we wish to present to-night is from a case of endocarditis, representing a type which as far as we know has hitherto not been described.

The best known forms of endocarditis are the rheumatic, syphilitic, acute bacterial, and subacute bacterial. We have introduced the designation "indeterminate" for an additional group of cases concerning which very little is known. This term is used to include (*a*) the cases of so-called terminal or cachectic endocarditis, and (*b*) a group of cases showing mural and valvular lesions of a peculiar type. The latter group we have designated as "atypical" or "atypical verrucous" endocarditis. In all probability, when these cases are better understood, a more appropriate nomenclature will be introduced.

A summary of the clinical history and autopsy findings of a case belonging to this atypical group follows. The patient was observed for a period of over four months.

S. H., female, aged twenty-four, married, was admitted to the Mount Sinai Hospital on January 21, 1922. (Admission No. 216669.) The only previous illness which she had had was an attack of polyarthritis three years before. Her present illness began six weeks before admission with sticking precordial pain. Two weeks later her ankles, knees, wrists, elbows, and shoulder joints became swollen and tender, but not red. She developed edema

of the face, which became so marked that her eyes were practically closed. The urine was scanty and her blood pressure elevated. A week before admission, she began to complain of sore throat. The edema of the face diminished, but the precordial and articular pain persisted.

On admission, the physical examination revealed petechiæ in the conjunctival mucous membrane of both lower lids, and also on the anterior aspect of the thorax and both sides of the neck. A systolic murmur could be heard over the entire precordium and left axilla. There was marked rigidity, tenderness, and pain in the left hypochondrium, symptoms pointing to splenic infarction. The spleen, however, was not palpable. The left elbow and the ankles were tender and swollen. The metacarpophalangeal joints of the left hand were painful and tender, but though there was no swelling, the overlying skin had a peculiar red color. There was erythema and induration of the skin and tenderness of the muscles, involving the extensor surface of both forearms. The face was slightly puffy.

The blood count showed red blood cells, 5,400,000; hemoglobin, 84 per cent.; white blood cells, 6,500; polymorphonuclear leucocytes, 84 per cent. The Wassermann reaction of the blood was negative.

In the week following admission, the articular pains improved and the dermatomyositis disappeared. The temperature continued to be elevated, reaching 101 to 103 daily. Albumin and casts were present in the urine, and there was persistent oliguria. At first there were no erythrocytes in the urinary sediment and the blood showed normal nitrogen figures; later, microscopic hematuria appeared and the blood showed moderate nitrogen retention. Crops of white-centred petechiæ recurred at frequent intervals. The articular pains returned and recurred from time to time. On February 8, a pericardial friction rub became audible, and on February 17, there was a return of the intense precordial pain from which the patient had suffered prior to her admission to the hospital. The temperature was now 104.4. In the meantime, signs of fluid in the chest appeared. On February 19, 250 c.c. of clear, yellowish fluid were withdrawn from the right side, and 20 c.c. of blood-tinged fluid from the left side. On the following day, the temperature fell to 99.8 and from this time on, with only occasional exceptions, the temperature remained below 101. Ascites now appeared, and signs of fluid in the chest returned. The patient had in the meantime become progressively more anemic, and on March 6, the red blood count had fallen to 2,088,000, and the hemoglobin percentage to 34. On March 10, a bed sore appeared over the sacrum and later others developed. The temperature now fluctuated around 100. From time to time the patient complained of severe abdominal pain, and vomiting with occasional hematemesis set in. On March 20, the patient became dyspneic, the albuminuria increased, and the breath was found to be uremic. The ascites had increased to such an extent that it was necessary to tap the patient. Accordingly, on March 22, 1,500 cu. cm. of clear, straw-colored fluid were removed from the peritoneal cavity. On April 4, the patient had a convulsion, following which she complained of severe precordial pain, and two days later she had a second convulsion. On April 19, a second abdominal paracentesis was necessary and this time 4,000 cu. cm. of fluid were withdrawn. On May 3, a diffuse herpes zoster appeared just below the left breast and scapula. The subcutaneous edema had now be-

come generalized, and the pericardial friction rub could again be heard. The temperature no longer rose above 99. In the last three weeks of her life, the patient frequently complained of severe epigastric and precordial pain. On May 31, she suddenly developed dyspnea and cyanosis. The pulse became rapid and irregular, and she became stuporous and died.

Four blood cultures were made, all with negative results. Special anaerobic methods were not employed.

It is evident that we were dealing with a patient suffering from a subacute febrile disease, and that some form of endocarditis was present. The clinical picture was unique. The main features were the glomerulonephritis developing at the onset of the disease, arthritis, dermatomyositis, petechiæ with white centers, infarction of the spleen, progressive anemia, nitrogen retention, absence of leucocytosis, acute pericarditis, peculiar red discoloration of the skin over some of the painful joints, Henoch's purpura, convulsions, and herpes zoster.

It was clear that the patient was not suffering from acute bacterial endocarditis. The question arose, was the patient suffering from rheumatic or a subacute bacterial endocarditis? In order to answer this question, it was necessary to evaluate the more important symptoms with a view of determining toward which of the two diagnoses each of these pointed. Petechiæ have not been encountered by us in proven cases of rheumatic fever. On the other hand, they occur in the great majority of cases of subacute bacterial endocarditis. Fibrinous pericarditis, on the other hand, does not belong to the clinical picture of the latter disease, whereas it frequently appears in conjunction with rheumatic endocarditis. Infarction of the spleen is very unusual in rheumatic endocarditis, and when it occurs has its origin not from the vegetations on the heart valves, but from a thrombus in the left auricle occurring in association with mitral stenosis. In our patient, there was no clinical evidence of mitral stenosis. Infarction of the spleen thus pointed toward subacute bacterial endocarditis. The repeatedly negative blood cultures, however, spoke against such a diagnosis.

Inasmuch as the symptoms did not fit in with either disease alone, the most probable diagnosis was a combined infection caused by the etiological agents of both rheumatic fever and sub-

acute bacterial endocarditis. If the atypical form of verrucous endocarditis had been considered at the time among the diagnostic possibilities, greater significance would have been attached to the negative blood cultures, the presence of dermatomyositis, and the ushering in of the disease by acute nephritis.

Summary of Autopsy Findings. The heart was somewhat enlarged and there was an organizing fibrinous pericarditis. On the tricuspid and aortic valves, there were a few small vegetations. The mitral valve showed diffuse thickening, pointing to a previous attack of endocarditis. On the line of closure, extending in places to the free edge, there was a row of grayish verrucous vegetations, more heaped up and more extensive than is generally seen in rheumatic cases (Fig. 1). In addition, the endocardium over the papillary muscles

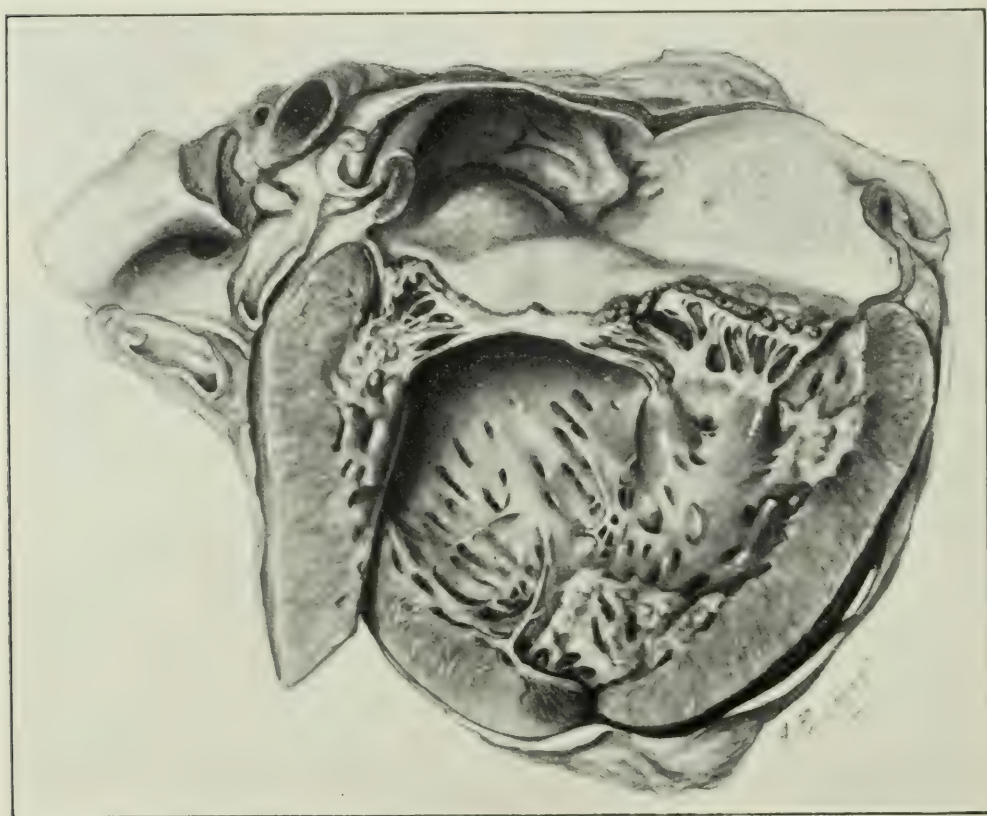


FIG. 1

and the mural endocardium between them was the seat of an inflammatory process. There had also been extension of the endocarditic process from the ventricular aspect of the posterior cusp downward for a short distance along the endocardium of the posterior wall of the ventricle. The surface in these areas was apparently denuded of its endothelium, and covered by extensive flat patches of thrombus deposit, the deeper layers of which were firmly attached to

the underlying myocardium. Near the apex of the ventricle there was a similar patch of mural endocarditis, of irregular outline, measuring 2.5 x 3.0 cm. The surface of the mural lesions was opaque, roughened, and irregularly fissured, the color being for the most part grayish or reddish-brown, with here and there a yellowish area. The heart muscle was brownish in color, pale, and showed fine grayish streaks.

The microscopic examination of the vegetations on the mitral valve showed lesions larger than those encountered in rheumatic endocarditis and the surface was only partially covered by endothelium. The blood platelet mass constituting the superficial part of the vegetation was larger than in rheumatic cases. The patches of mural endocarditis showed extensive deposition of hyalinized blood platelet thrombus, the greater part of which was not covered by endothelium. In the subendothelial layers of all the endocarditic lesions, there were collections of round cells. Marked fibrosis was seen in the deeper layers of the vegetative masses of both the valvular and mural lesions, indicating extensive healing. In the case of the mural patches, the fibrous tissue invaded the underlying myocardium rather deeply, destroying and replacing many of the muscle fibers. There were no bacteria to be found in the vegetations, nor were Aschoff bodies or Bracht-Waechter lesions present in the heart muscle.

The remainder of the post-mortem findings will be stated briefly. There was bilateral organizing fibrinous pleurisy with fluid in the left pleural sac, congestion and edema of the lungs, edema of the lower extremities, and decubitus ulcers over the sacrum. The kidneys were the seat of a subacute diffuse glomerulonephritis. The spleen contained one small infarct, but was not enlarged.

A glance at the heart from this case suffices to convince one that the lesions do not correspond to those found in either rheumatic or subacute bacterial endocarditis. The vegetations differ in morphology and localization from those seen in rheumatic endocarditis and Aschoff bodies are absent from the myocardium. The failure to find the Aschoff bodies is not conclusive, however, inasmuch as they are not always present in rheumatic cases. Of greater significance is the occurrence of splenic infarction in the absence of a thrombus in the left auricle.

The endocardial lesions differ from those found in subacute bacterial endocarditis in their morphology and distribution, and in the absence of bacteria even from the fresh parts of the vegetations. Furthermore, the myocardium shows no Bracht-Waechter bodies, and the kidneys no embolic glomerular lesions. Acute diffuse glomerulonephritis occurs in subacute bacterial endocarditis, but not at the onset of the disease. On the other hand, the fibrinous pericarditis which developed long before the patient

showed nitrogen retention (which was never very marked) speaks against the latter disease.

To summarize, the patient suffered from a condition that does not correspond to the usually recognized forms of endocarditis. We have had the opportunity of observing three other cases, the results of which will be published in connection with the one discussed to-night. It must be left to future studies to determine whether all of these cases are due to the same cause, and whether they are due to an undescribed virus or are the extraordinary results of a known etiological agent.

CARCINO-SARCOMA OF THE UTERUS

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(From the Pathological Laboratory of the Lenox Hill Hospital)

Claessen and Mathias¹ in a recent general review of the subject of carcino-sarcoma have collected seventy-three cases which they accept as authentic. The organ distribution of these neoplasms was as follows: uterus, 20; breast, 15; ovary, 12; thyroid, 7; esophagus, 4; stomach, liver, lung, kidney, 2 each; gall bladder, pancreas, pharynx, tube, prostate, nose, 1 each.

The age incidence varied, the earliest case being two years of age, with the greater number of cases occurring in the fifth decade of life.

The symptomatology was that of malignant tumors in general. The organ incidence demonstrates quite clearly that the majority of cases have occurred in the female sex.

Ewing² in a discussion of carcino-sarcoma of the uterus says that the interpretation of these cases has given rise to much discussion. Thus, simultaneous occurrence of two separate tumors, which constitutes the most frequent and least notable form of the combination, has been observed, while in other instances two tumors have arisen separately, but later one invaded the other. Occasionally, at the point where a submucous or mural sarcoma meets the glandular layer, carcinoma develops secondarily. The glands included in sarcomatous polyps, or in inflammatory polyps,

or in adenomyoma may become carcinomatous. Spurious cases are undoubtedly recorded in which a typical proliferation of glands was interpreted as carcinoma, or endothelial proliferation was so mistaken; or in which carcinoma, becoming diffuse and its cells assuming a spindle form, bore a certain resemblance to sarcoma.

The most recently reported case of carcino-sarcoma of the uterus is that of Klee.³ In this case the tumor apparently originated in the cervix and the sarcomatous elements arose in the stroma of the cervical carcinoma and continued their growth into that portion of the uterus not involved in the carcinoma.

The present case resembles that reported by Klee. A female aged fifty-two years presented herself with the usual clinical history of a malignant uterine growth in which the symptom of metrorrhagia had persisted for four months. An hysterectomy was performed.

The gross specimen consisted of a uterus measuring 14 x 7 cm., the vaginal portion of which was destroyed and replaced by a crater-like ulceration lined

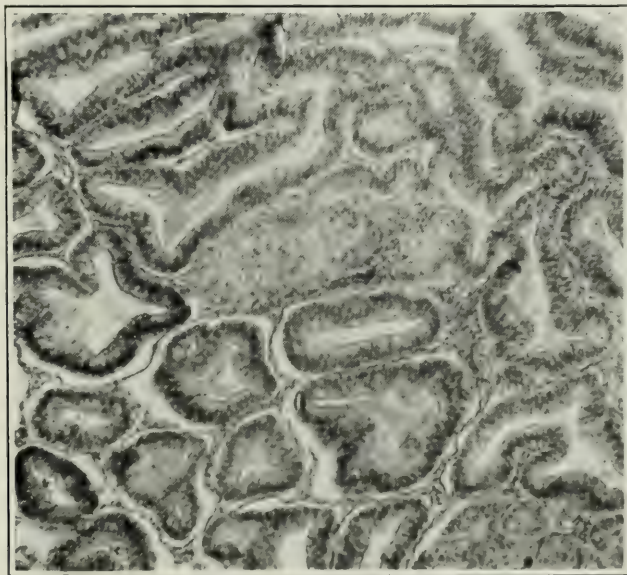


FIG. 1

by a grayish membrane. Upon section it was evident that a neoplasm had destroyed the cervix to within 3 to 4 mm. of the internal os. Extending from the internal os was a yellowish band about 8 mm. in thickness situated directly beneath the mucosa and extending on all the surfaces of the uterine cavity up to within 2 cm. of the uterine cornu. There was no ulceration except at the

cervix. A definite mass in the uterus was not demonstrable, the neoplasm extending rather as a broad sheet.

Microscopic examination showed at the cervix beneath the layer of necrotic material and debris an adenocarcinoma (Fig. 1) in which the neoplasm was composed of rather large regular acini lined or filled by epithelial cells of the low columnar variety, a fair number of which contained a mucoid secretion. These acini were separated from one another by a delicate stroma of non-cellular character. Sections taken from the upper portions of the neoplasm near the cornu of the uterus showed beneath a normal mucosa, a broad sheet of spindle-shaped connective tissue cells (Fig. 2) in which intracellular fibrils were demonstrable.



FIG. 2

In the region about the internal os, and just above it, there were areas of frank sarcoma in which there were acini of neoplastic epithelial cells and areas of frank carcinoma in which there were islands of sarcomatous cells. In this region it was possible to demonstrate numerous areas in which the delicate stroma supporting the epithelial acini was assuming malignant properties as evidenced by the altered staining reactions of the cells, their increased size, irregular shape, and the frequency with which mitotic figures were observed.

In general, the sarcomatous elements far outnumbered the carcinomatous ones, the latter being found only in the cervical region. The sheet-like appearance of the tumor in the gross and the areas of transition from benign to malignant stroma as seen

in the cervix incline us to the opinion that the specimen is one of true sarcomatous degeneration of the stroma of a carcinoma rather than the admixture of the two distinct tumors.

(I am indebted to Dr. Wm. Freile of Jersey City, N. J., for pathological material.)

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Discussion:

DR. MOENCH: Many of these so-called carcino-sarcomata are not carcino-sarcomata at all. I have seen three uterine tumors which at first appeared to be carcino-sarcomata until serial sections proved them to be merely atypical carcinomata. One of them was especially misleading. It was seen by men as well known as Paul v. Baumgarten and diagnosed as a perivascular sarcoma. We found, however, that it too was nothing but a perivascular infiltration of the carcinomatous cells, and that the character of the cells had changed, possibly due to pressure or due to some other causes we know nothing about. I would like to ask if serial sections of the tumor were made to see if any transitional stages of the two types of growth were present.

DR. ROHDENBURG: We have not made serial sections, but we took serial blocks and cut ten or fifteen sections from each block. We have not been able to find any place where there was a gradual change, and the demonstration by the Bielschowsky method of intercellular fibrils rules out the possibility of transformed epithelium.

DR. PAPPENHEIMER: In the reported cases, have the metastases shown a mixture of both elements, or had one overgrown the other?

DR. ROHDENBURG: In some cases the sarcoma has outgrown the carcinoma, and in others the carcinoma has outgrown the sarcoma.

DR. MACNEAL: It seems to me a tumor of this sort presents an interesting problem as to whether the two malignant portions may have arisen in relation to each other or in entirely separate situations. The possibility of separate origin is suggested in the slides here because in one portion there is a purely epithelial tumor, and in others a purely connective tissue tumor, and in still others a mixture of the two types. In an organ such as the uterus, where carcinoma is so frequent, the occurrence of a sarcoma might very well be associated with carcinoma developing independently. The only example that has occurred in our service at the Post-Graduate Hospital in ten years in which a possible mixture of carcinoma and sarcoma had to be considered was a breast amputated for carcinoma. There was a recurrence in the scar which was excised by the

surgeon with the clinical diagnosis of recurrent carcinoma. This, however, proved to be a sarcoma. This case was of some international interest, as the patient was a relative of a physician in a foreign country, and the slides had to be sent abroad to confirm this very bizarre diagnosis. This is the only example of epithelial and connective tissue tumors which I recall in which there was not a very definite separate origin of the two tumors. I think the combined tumors of separate origin are more common.

DR. ROHDENBURG: It is perfectly possible that this may be a primary sarcoma arising in the stroma of the mucosa, which subsequently in some fashion that we do not yet understand caused a malignant transition of the epithelial cells, but the fact that in some of these sections there are areas in which perfectly normal stroma showed a gradual change into a malignant type of stroma has made me feel that it is an actual transition of the stroma rather than two distinct tumors which have merged one into the other.

THREE CASES OF METASTATIC NEOPLASMS OF THE HEART

JAMES R. LISA, M.D.

The first case, J. F., was a white male, fifty-seven years old, who was admitted to the Hospital on June 14, 1920, complaining of ulceration of the cheek and tongue. His father was said to have died of carcinoma of the throat. The patient stated that eighteen years ago he had an ulcerated tooth, and treated it by mouth washes, but without result. Five years ago the lymph glands of the neck began to enlarge, and five months ago ulceration began on the left cheek, gradually increasing in size until it attained the diameter of three inches. Otherwise the history was negative.

Physical examination showed an elderly white man with an ulceration perforating the left cheek, the edges being raised and hard. The tongue was likewise involved by a similar ulceration. The neck glands were enlarged, matted together, and adherent to the skin. A biopsy wound was infected, and discharging a foul, thick pus. The heart sounds were irregular and weak, and there was a marked general arteriosclerosis. Death occurred on June 15th.

Autopsy was performed twelve hours after death. The findings in the heart (Fig. 1) were as follows: The weight was 460 gm. In the right ventricle was a very firm, white, slightly nodular mass measuring 2.5 cm. in diameter, sharply demarcated from the cardiac muscle, and not encapsulated. The surface was eroded, the endocardium apparently being destroyed. The other findings were those of an interstitial myocarditis, a thickening of the mitral and aortic cusps, and arteriosclerosis of the coronaries, these, however, being patent. The summary of the other findings was carcinoma of the tongue and cheek with involvement of the left cervical lymph glands, bilateral hydronephrosis, syphilitic aortitis, and bronchopneumonia.

Microscopic examination showed the cardiac tumor to be composed of

smaller and larger masses of large polyhedral and spindle cells with a marked tendency to whorl formation. The cells at the periphery of the whorls were flattened with flattened, oval, hyperchromatic nuclei. Toward the center the cell outlines became indistinct and the nuclei hypochromatic. The centers were homogeneous and stained a bright red. There were no mitotic figures. The tumor cells invaded the intermuscular tissue at the periphery of the tumor, and the cellular infiltration beyond them was small lymphocytic in character with a few eosinophilic cells. The cardiac cells beyond the zone of cell reaction were granular and lighter staining than normal, and the nuclei swollen and pale. The endocardium was lost over the surface of the tumor, and a layer of fibrin containing a few polymorphonuclear cells replaced it.

The diagnosis of squamous cell carcinoma, metastatic from the tongue, was made.

The second case, D. S., a white male, aged forty-two, was admitted March 11, 1921. His history revealed the fact that about one year before admission a black growth had appeared in the upper jaw, increasing in size rapidly to that of an egg. He was treated with radium, and later the right incisors were removed and the bone curetted. Seven months later the cervical lymph nodes began to enlarge, and three months afterwards subcutaneous masses developed over the entire body and the abdomen commenced to enlarge.

Physical examination revealed a jet-black area of the buccal mucosa above the right incisor teeth with several smaller black areas in other parts of the mouth. There were very many small, firm, freely movable subcutaneous masses scattered over the entire body. The cervical lymph nodes of both sides were enlarged. The abdomen was distended with fluid, and a very tender mass was felt in the epigastrium. The heart sounds were weak, but otherwise negative. Death occurred on April 13, 1921.

Autopsy was performed on April 14, 1921, ten hours after death, by Dr. John H. Larkin and the author. The heart (Fig. 2) was found studded with small white firm nodules sharply demarcated from the surrounding cardiac muscle and subepicardial, intramural, and subendocardial in location. The mucosa of the mouth showed the lesion described above. There were metastases to the subcutaneous tissues, lungs, trachea, liver, spleen, kidneys, pancreas, stomach, large and small intestines, omentum, and ribs.

Microscopical examination showed the tumor removed from the heart to consist of a mass of large cells of various shapes, round, oval, and polyhedral, with large round or irregularly oval nuclei, the majority hyperchromatic, a few hypochromatic. Several large multinucleated cells were present. Mitotic figures were frequent. The tumor was rather vascular, and tumor cells were present in the lumina of the vessels at the periphery. Pigment-bearing cells were very infrequent and found only in one portion near the periphery. The outlying cells had invaded the connective tissue between the cardiac muscle cells. There was only a slight lymphocytic cell infiltration of the adjacent tissue.

The buccal mucosa had lost its epithelium immediately over the heavily pigmented area. Here the tissue consisted of a rather loose vascular connective tissue with very many large oval or irregular cells having large heavily staining nuclei. Many of the cells were so heavily laden with a golden brown or black

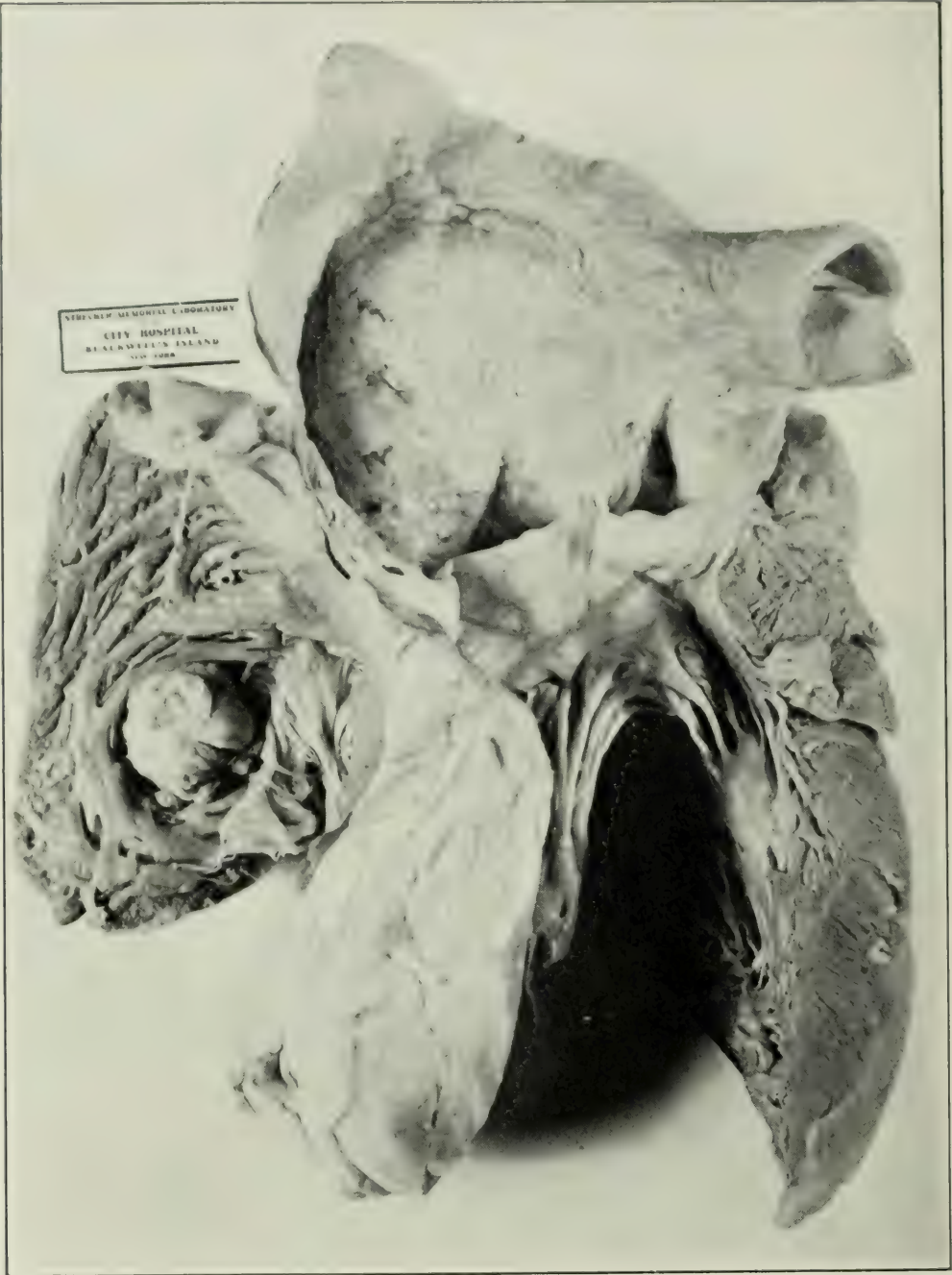


FIG. 1. Case 1

pigment that the nuclei were entirely hidden. In other cells the pigment was finely granular, and obscured, but did not hide, the nuclei. At the edges of the section the epithelium was intact, thicker than normal, and the stratum germinativum had an occasional mitotic figure. The corium beneath showed a few scattered pigment-bearing cells.

The diagnosis in this case was melanosarcoma, metastatic from buccal mucosa.

The third case, A. B., was a white male, aged fifty-four, who was admitted on January 2, 1923. The family and personal histories, up to the onset of the present illness, were negative. Three weeks before admission the patient had become ill with severe abdominal pain beginning immediately after eating and followed by vomiting. The pain increased in intensity, and on admission was present almost continuously. The vomitus contained blood at intervals.

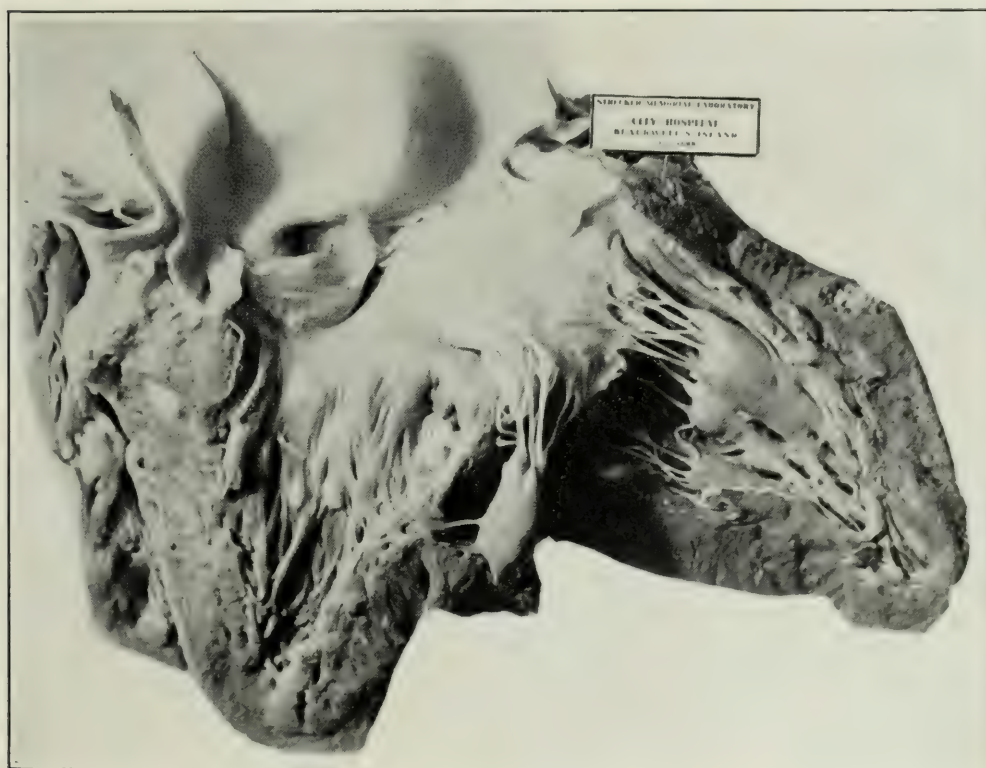


FIG. 2. Case 2

The physical examination showed marked emaciation, slight jaundice, many freely movable subcutaneous masses, enlarged left supraclavicular lymph node, irregularity of the heart sounds, with apical systolic and double aortic murmurs, palpable liver, and a large, irregular, hard, painful epigastric mass. A few days before death the patient developed a very intense jaundice. He died on January 15, 1923.

Autopsy was performed four hours after death. The heart showed several small, round, and oval firm white masses lying in the edematous fat along

the coronary vessels in the right interventricular groove, the atroventricular sulcus, and one involving the outer surface of the left auricle. There were no intramural or subendocardial growths. The other autopsy findings were diffuse carcinoma of the stomach and metastases to the regional lymphatics, the thoracic and cervical lymph nodes, the adrenals, the kidneys, omentum, mesenteric lymph nodes, and the subcutaneous tissues.

Microscopical examination showed the tumor removed from the coronary fat to consist of a nest of large polyhedral cells with large round and oval hyperchromatic nuclei lying in a loose connective tissue network and with several normal fat cells still present. Some of the nuclei were extremely large and vacuolated. A few of the cells were vacuolated and the nuclei pressed out at the periphery into a crescent shape. Mitotic figures were fairly frequent. Some of the sections showed an extreme loss of the tumor cells, the connective tissue network only remaining.

The stomach showed a similar picture, the loss of cells, the crescent-shaped nuclei in vacuolated cells, and the mitotic figures being more marked.

The diagnosis was colloid carcinoma, metastatic from the stomach.

Besides the comparative infrequency of metastatic neoplasms occurring in the heart, these cases have two other interesting features. The primary sites—tongue, buccal mucosa, and stomach—are among the more unusual locations of the primary tumors, the most common being intrathoracic according to Blumensohn¹ and Cornil.²

The involvement of the heart may occur by direct extension, the common mode in intrathoracic neoplasms, by the blood stream, or by the lymphatics. In case 2, the multiple tumors and their widespread involvement of the heart clearly indicate that the metastases have occurred through the coronary circulation. In case 3, the lymphatics apparently are the source. In case 1, two possibilities must be considered, metastasis through the coronary circulation and direct implantation on the endocardium. The features of the tumor being single, its location in the right heart, the destruction of the endocardium, and the absence of pulmonary involvement lend support to the latter explanation.

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1. BLUMENSOHN: *Metast. Malign. Geschwult. in Herzen*, 1907.
2. CORNIL: *Étude sur le Cancer de Coeur*, 1902.

TUBERCULOUS OVARIAN CYSTS WITH A REPORT
OF A THIRD CASE OBSERVED BY THE AUTHOR *

G. L. MOENCH, M.D.

*(From the Department of Gynecology and the Department of Pathology and
Bacteriology of the New York Post-Graduate Medical School
and Hospital)*

Abstract

Tuberculosis of the female genital tract is a common disease which is found especially in the uterus and tubes. The ovary on the other hand seems to be fairly immune. Most authors agree in this respect, as the percentages of ovarian involvement are usually well below 33, although some men give higher figures. The latter are usually based on rather small series.

At the New York Post-Graduate Medical School and Hospital only seven cases of ovarian tuberculosis have been seen since 1913. In my own experience also such cases have been rare. Nevertheless, some pathologists believe that tuberculosis is especially prone to cause ovarian cysts, and some even go so far as to state that the non-specific inflammation, seen at times in such ovaries, is a real tuberculosis which has lost its characteristic histological appearance.

Personally, I must say that I can not gain the impression, either from the literature or from my own experience, that tuberculosis is very frequently associated with ovarian cysts. Furthermore, ovarian cysts with the typical picture of tuberculosis, while very rare, do occur, so that it can not be said that the ovarian tissue reacts differently from the rest of the body to the tubercle bacillus.

Up to 1916, as far as I could learn, only thirty-two cases of ovarian tumors, infected with tuberculosis, had been reported in the literature. In this list were two cases of my own. The first of these was a large serous cyst of the left ovary with tubercles in its wall. The peritoneum showed a very advanced tuberculous condition; the uterus and tubes, however, were not infected.

* The paper in full with bibliography will appear in *Am. Jour. Obst. and Gyn.*, October, 1923.

The second case was a solid fibro-adenoma of the left ovary containing many tubercles and accompanied by a tuberculosis of the uterine mucosa and the tubes, but without a peritoneal tuberculosis.

Since that time (1916) only one other case, that of Forgue and Chauvin in 1919, has been reported in the literature.

Among these thirty-three cases of tuberculous ovarian neoplasms seven were intraligamentous, about a dozen were dermoid cysts, and only two (Glockner's case and my second one) were solid.

I realize that many more than thirty-three cases of this type have been reported in the literature, but a close examination will reveal that such cases are either not ovarian neoplasms or have not been examined carefully enough to allow of an opinion as to their true character.

At the Post-Graduate Hospital I recently saw a thirty-fourth case of a tuberculous ovarian tumor. This patient (chart number 26431, pathological number 7064-14065) was a nulliparous married woman of twenty-nine years of age. She had a mass on the left side of the abdomen extending almost to the umbilicus and projecting downward into the cul-de-sac of Douglas. Operation revealed a dermoid cyst on the left side and large bilateral pyosalpinges. The right ovary was normal in size, the peritoneum was not diseased, but there were many old firm adhesions present. The adnexae of both sides were removed.

Pathological examination showed a bilateral tuberculous salpingitis, a tuberculous infection of the wall of the dermoid cyst and a small cystic degeneration of the right ovary which was free from tuberculosis.

The mode of infection in cases of tuberculosis of ovarian cysts is either by direct contact, that is, through the lymph channels from the diseased uterus, tubes or peritoneum, or by the hematogenous route. A third possibility is the infection of the cyst-wall or contents through tapping in the presence of a tuberculous peritonitis. This third mode of infection naturally was more common formerly when ovarian cysts were tapped as a routine. Another condition that must be thought of is a primary tuberculosis of the ovary. This, however, is not probable in any case and always extremely difficult to prove.

Discussion:

DR. SCHWARZ: I think the figures that Dr. Moench has given in regard to the proportion of cases of tuberculosis of the ovary and tube are probably correct. Tuberculosis of the ovary is very rare indeed in comparison to the frequency of tuberculosis of the tube. Also the ovary is not so easily affected by inflammatory processes. The actual involvement of the ovary itself, or the infiltration of the ovary, is the exception; the rule is perioophoritis, when the usual diagnosis of salpingo-oophoritis is made. If tuberculosis invades the ovary it probably invades it through the hilus, but then it travels against the lymph stream. The hilus vessels drain through the mesosalpinx into the large lymph vessels. So if a tuberculosis of the tube invades the ovary it has to go against that stream, and it is possible that that is one of the reasons why the ratio is probably 1:25 or even less than that. I have seen only once tuberculosis of the ovary without tuberculosis of the tube; otherwise it is always secondary to tuberculosis of the tube, and even in the presence of tuberculosis of the tube, the ovary is seldom affected, so that the statistics that Dr. Moench has given of 85 per cent. of cysts in the French literature are certainly incorrect. The small cystic "degeneration" is unlikely to be of inflammatory origin. The dermoid cysts are rather susceptible to tuberculosis. In one case I found a so-called pseudo-tuberculosis. This is found in dermoids rather frequently, and resembles actual tubercles with a few foreign body giant cells, so possibly a number of the cysts reported in the early literature of dermoids combined with tuberculosis were simply giant cells embedded in some pseudo-tubercles, such as one sees frequently if one makes enough sections of dermoids. These formations are due to a reaction caused by the transportation of fat from the dermoid.

DR. MOENCH: The reason I laid so much stress on the statistics secured by some men is that Greenberg in the Johns Hopkins Hospital Reports claims to have found an involvement of the ovary in 33.1 per cent. of all cases of tubal tuberculosis.

As to the theory of follicular cysts being produced by tuberculosis, I believe we can eliminate that without much discussion, because it is pretty well proven that follicular cysts are not inflammatory at all, but are based on circulatory disturbances in the ovary which allow numerous follicles to develop synchronously, but not to reach maturity on account of the ensuing formation of a corpus luteum. In dermoid cysts we do find giant cells, but they are in the epithelium and not in the actual stroma of the wall of the dermoid cyst, as the process is in this particular case.

AN EPENDYMAL GLIOMA OF THE SPINAL CORD

LEON H. CORNWALL, M.D.

The patient from whom this tumor was taken was a female aged seventy-one years. The pertinent points in the history were as follows:

For four years previous to admission to the hospital she had suffered with persistent pain in the right hip, occasionally extending into the thigh. Shortly after the onset of this symptom the patient had a fall while walking in a dark room causing considerable trauma of the face. During the four years she had visited the out-patient departments of several New York hospitals. In each case the diagnosis of arthritis had been made and at one of the institutions a cast was applied. The family history showed that her father had died at the age of seventy-four from cerebral hemorrhage and one brother at the age of fifty-two from the same cause.

The patient had been able to perform her regular household duties until two days before admission to the hospital. The onset was sudden. While undressing she experienced very severe pain in the abdomen and right hip. Almost immediately following she became weak in both legs. On the following day it was discovered that the patient was completely anesthetic from the hips down. This finding was confirmed after admission to the hospital. In addition the history records a flaccid paralysis of both legs with absent deep reflexes, incontinence of urine and feces, and muscular atrophy in both lower extremities. Death ensued nine days after admission, the immediate cause being terminal pneumonia.

The autopsy revealed a large extra-dural hemorrhage confined to the lower dorsal and lumbar region of the spinal cord. This hemorrhage was most extensive over the dorsal surface. On sectioning the cord in the lower dorsal region degeneration of the lateral and dorsal columns could be detected grossly. The other gross anatomical diagnoses were bilateral lobular pneumonia, ascending urinary infection, chronic passive congestion of the liver, senile atrophy of the spleen, chronic interstitial pancreatitis, polyps of the cervix uteri, general arteriosclerosis, and chronic myocarditis.

Microscopic examination of the cord showed an extreme variability in the central canal. In the cervical region it was patent and the ependymal cells had a regular arrangement quite similar to that seen in infants. In the upper dorsal region the lumen was obliterated, while in the mid-dorsal region it again became patent. The hemorrhage had dissected upwards to approximately the mid-dorsal region. Both the pachy- and leptomeninges were thickened, more so on the dorsal than the ventral surface of the cord. The pial arteries were all injected and the veins, more especially at the dorsal sulcus and the ventral fissure, were thrombotic. Just below the mid-dorsal region of the cord there was an increase in the ependymal cells. They were heaped up in several layers and small cell groups of from three to six cells and could be seen completely detached from the area around the obliterated central canal. Some of these groups had a rosette arrangement. In the lower dorsal region all four horns were involved by a neoplasm. The cells were arranged singly and in small groups. Some

of the groups had a rosette arrangement and others showed a tendency to the formation of whorls. The cells were of various sizes from the small pycnotic to typical adult glia cells. In some areas the cell groups surrounded small thin-walled capillaries.



FIG. 1. Showing the arrangement of the ependymal cells around the central canal in the cervical region

The nuclei were variable in size and shape, some being round or oval, and others irregular and kidney-shaped. Many cells contained two or more nuclei. Some of the nuclei were central in location and others eccentrically placed. The staining reactions of the nuclei likewise showed considerable variability, some being deeply stained and containing a fairly dense chromatin network, whereas others were hypochromatic. There was an increased vascularity in both the gray and the white matter. Small, thin-walled capillaries were especially abundant in the gray matter. The ganglion cells of the ventral horns were absent in the tumor region but in adjacent segments above this level showed various degenerative changes. Many of the cells that remained showed complete loss of tigroid except around the periphery of the cell (central chromatolysis). The nuclei of many cells were eccentric and the dendrites were short and stubby (atrophy). In others both the nuclei and tigroid had disappeared entirely and the cells were small and elongated.

There were groups of cells in several of the dorsal and ventral veins which in their morphology resembled the tumor cells described above. These were interpreted as tumor emboli.

In the immediate vicinity of the tumor there was extensive demyelination of the white matter except in the juxtargiscal zones of the dorsal, lateral, and ventral columns. The white matter had a honeycombed appearance but there was practically no ascending or descending degeneration. The changes in the white matter were not accompanied by inflammatory reaction but were similar to those seen in myelomalacia.

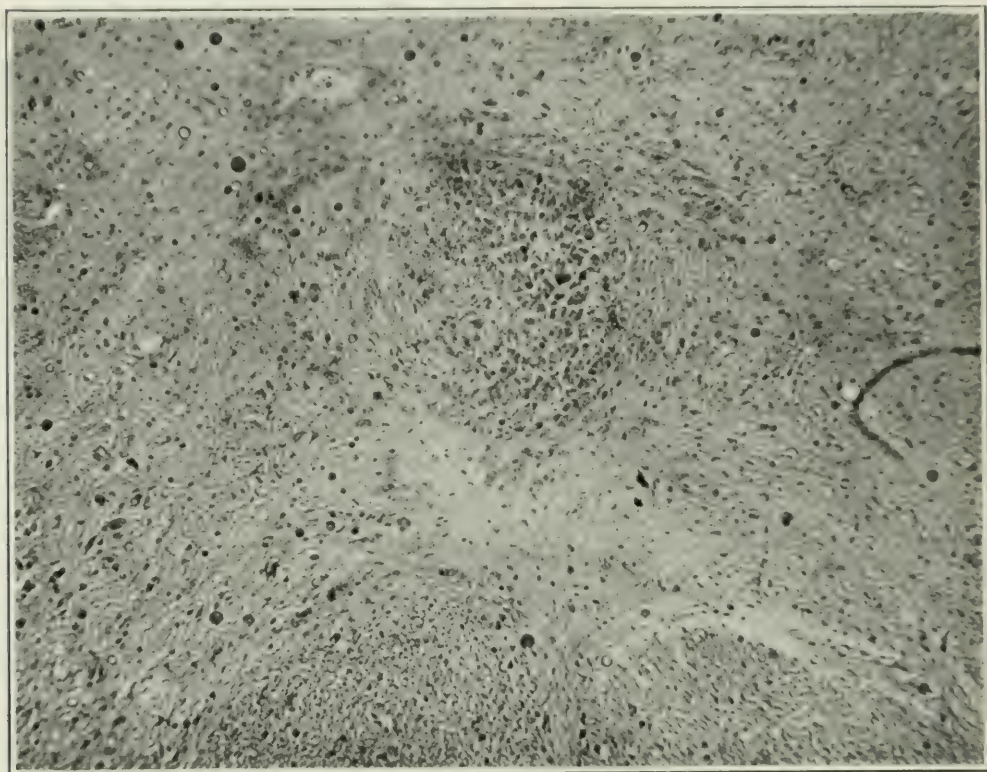


FIG. 2. Showing the region of the central canal just above the tumor

The histopathology of this tumor justifies its classification as a glioma originating from the ependyma. All stages in the life history of the glia cell may be seen in the sections.

The duration of the tumor is a matter of speculation but it probably was slow in developing and the symptom of pain that was first noted four years ago would lead one to the conclusion that the afferent fibers carrying this type of sensation were compromised at that time.

The slight degree of incapacity that was occasioned by such extensive pathological changes involving all four horns as well as the dorsal, lateral, and ventral white columns is significant. This apparent inconsistency between functional impairment and struc-

tural alteration is not uncommon in gliomata, the probable reason being that the loose structure of the tumor allows many nerve fibers to course through it without being damaged sufficiently to impair their functional activity.

Sudden hemorrhage is also not uncommon in gliomata, but the extra-dural location is hardly what might have been expected. Tumor emboli are not common in gliomata and in this respect the case is unusual. It is probable that the sequence of events was embolism, thrombosis, and hemorrhage.

THE BRAZILIAN CONTRIBUTION TOWARDS THE IMPROVEMENT OF THE SPECIFIC SNAKE BITE TREATMENT

AFRANIO AMARAL, M.D.

(*Butantan, Brazil*)

I am very glad to have received your invitation to address you on the progress of the anti-ophidic serum-therapy in Brazil, because the opportunity is favorable to call your attention to the necessity of a closer understanding between the people living in the United States and those living in Brazil, and especially between North American and Brazilian scientists, and because I only have to summarize the arduous work undertaken by my own Institute during a quarter of a century.

About twenty-five years ago Vital Brazil, the former director of Butantan, following in a different manner the immunological investigations of Calmette, Sewall, Kaufmann and Bertrand, and Phisalix with snake venoms, went into the field of practical application by preparing four sera, the activity of which was very marked in the case of Brazilian snake bites. His studies were continued by Florencio Gomes, one of the finest scientists I ever met, whom I succeeded in the Snake Department of the Institute.

Butantan, a purely Brazilian scientific institution, is at the present time not only capable of curing the most severe cases of snake poisoning which take place all over the territory where it

is located, but also of stating that the application of its methods will be successful in the preparation of antitoxins for any kind of snake venom.

The most important feature of our task comes from our having faced a great many momentous questions in order to make the actual decision which means the definite solution of one of the hardest problems prevalent in many tropical countries. These questions were concerned with the people who live in the country and who have a very superstitious turn of mind, and with the species of snakes existing there, most of which were almost completely unknown from the scientific standpoint. Consequently, we had to make a wide propaganda, distributing pictures, pamphlets, and books, contributing in this way to educate the people.

We established individual measures of protection for those who helped us in our campaign and we developed a general prophylactic system of advising everybody not to go around bare-legged; by freely distributing boxes, cages, and *lassos* for catching snakes and sending them alive to the Institute, and finally by improving the methods of making antitoxins.

We succeeded in this manner in receiving an increasing number of snakes whose annual average is now above 10,000, three quarters of them being venomous; at the same time the death rate from snake poisoning has decreased and is kept within negligible limits.

When we started the campaign incomplete statistics of the State of S. Paulo showed an average of 150 deaths a year from a total of about 1,500 snake bites. Now the annual death rate is reduced to only three or five cases, which, of course, are due to improper treatment, such as the prescription of "medicines" like kerozene and alcohol by incompetent people, charlatans, and "doctors by correspondence."

If we compare these figures with those of India where the system of killing snakes and paying for their heads, which has been largely advocated and so far used by the English authorities, has failed to decrease the death rate from 20,000 or 25,000 a year, we can easily comprehend the difference in the efficiency of

the two methods. Our idea in Brazil is to capture every snake in order to make use of it, namely, in supplying us with the much needed antigen for horse immunization. Englishmen, however, have not applied in India other measures of prophylaxis, especially the one regarding the improvement of the conditions prevalent in the fields, forests, and so on, which is very necessary; inasmuch as the campaign there is based on the systematic destruction of serpents, they are just trying to fill up a large bottle without a bottom.

In addition to this, we believe we have contributed also to the advancement of the biology of *Ophidia*, whose geographical distribution in Brazil has been carefully studied, and to the differentiation of the characteristics of their venoms and of the various types of poisoning.

After many attempts, we succeeded in settling upon a good technique with regard to antitoxin preparation, the different stages of which may be summarized as follows:

1. Venom extracting which is done in the manner indicated in the slides.
2. Dissolving venom in equal parts of normal saline solution and glycerine.
3. Titrating venom by the use of pigeons and other small animals.
4. Immunizing horses, which is carried on by subcutaneous injections of gradually increasing doses of venom every three or five days. Two processes are used for this purpose: The *slow process* is continued for about six months and consists of very small doses of venom at the beginning, from 0.05 mg., 0.06 mg., 0.10 mg., gradually increasing until 0.5 gm. At the end of the sixth month a horse may resist a dose about 10,000 times larger than the initial one. The *quick process* is continued only for about two months and consists of larger injections of venom neutralized by the specific antitoxin (neutral mixture), the first injection being of 0.01 mg. venom + q. s. antitoxin.

From the immunization standpoint, we do not advocate Calmette's method of reducing the toxic activity of the venoms by

the destruction of their toxophorous group by means of chemical substances. The transformation of the venoms into toxoids which probably involves changes in the qualitative components of the venoms may be responsible for the weakness and even lack of activity of many of the antivenomous serums sold by commercial concerns.

Going back to the antitoxin preparation, we have the following stages:

5. Preliminary bleeding of the horses for titrating their serum. This must be done seven days after a dose of about 0.4 gm. or 0.5 gm. has been given in a single injection.

6. Successive bleedings of the horses, followed by injection of large amounts of venom. This must be done only when the horse serum shows a high degree of antitoxic activity towards the venom used in the immunization process. In bleeding horses, we separate the blood plasma.

7. Refinement and concentration of horse plasma to remove toxic substances from it, namely, serum, seralbumin, etc., to reduce the total amount of liquid to be injected in a single dose, and to increase the strength of the product.

We have undertaken many experiments with the different fractions of precipitated plasma of horses immunized either with snake poisons or with scorpion venom, and we have finally come to the conclusion that the antitoxins in these cases are, during the concentration process, carried by the pseudoglobulin.

The refinement and concentration of the serum to from six to twelve times its original strength are easily performed. The antitoxin vials are distributed to the people in a philanthropic way, in exchange for living snakes.

8. Antitoxin titration. One of the greatest difficulties in securing active antitoxins lies in the choice of a good method for testing them. Vital Brazil tried a direct reading method which is now largely used for this purpose in Brazil. Ehrlich's method for titrating diphtheria antitoxin is as you know based on a *standardized* and fixed quantity (L + or *limes mortis*) of toxin mixed with variable quantities of the antitoxin to be titrated, but

the direct reading method consists in mixing a fixed amount of antitoxin (1 c.c.) with variable amounts of toxin (venom). The mixture is placed in the incubator for about thirty minutes and is injected intravenously into pigeons. When the antitoxin is strong enough it completely neutralizes the toxic properties of the venom, and the pigeon does not show any symptom of poisoning. The results obtained by this method are exact, fixed, and accurate and completely succeed when applied to the treatment of humans.

As far as the antitoxin activity is concerned, we do not agree with Calmette's opinion in considering a serum coming from a horse immunized against a kind of hemolytic or neurolytic snake venom as effective for accidents caused by every kind of hemolytic or neurolytic snake venoms. Calmette's serum has, in effect, no activity either towards the venom of any Brazilian species, according to V. Brazil's and my own experience, or, according to Ditmars' observation, towards the bites of *C. atrox*, which is one of the commonest rattlers in this country.

We agree with Phisalix's and Bertrand's point of view in accepting the principle of specificity of the antitoxin. This principle, although recognized in directing the proper prescription of venom antitoxins, is not very strict however, since we know now that antitoxins are able to arrest the deleterious effects of the venoms of snakes closely related to that to whose venom the antitoxin is specifically effective. For instance, an antitoxin specific for *Bothrops jajaraca* is active to a certain degree against the venom of other closely allied species, such as *B. jararacussu*, *B. atrox*, and also *B. insularis*, a species I studied, which lives on an island far from the coast of the State of S. Paulo. The antitoxin for *Crotalus terrificus*, the South American rattler, has been shown to be useful for bites produced by the North American *C. atrox*, according to a very interesting observation made by Mr. Ditmars, Dr. Van der Smissen, Dr. V. Brazil, and Dr. George Semken.

The victim, a keeper in the Bronx Park Zoological Gardens, was bitten on January 27, 1916, by a large diamond back rattler

and was injected with Calmette's serum, but without result. Another serum was then procured from Dr. V. Brazil who was at that time in this city. Ditmars, who described this case in the May, 1916, issue of the *Zoological Society Bulletin*, gives the following opinion about the patient's recovery and the antitoxin action on him: "Within a few hours there was complete cessation of vomiting and chills. Within twelve hours the greatest swelling that had involved the arm and a considerable portion of the body had decreased one third, by actual circumference measurement of the arm, and it rapidly receded from the breast. The area of intense discoloration also faded. Return to a normal mental condition with increase of vitality followed these changes." "The treatment of the case of Keeper Toomey demonstrates the fact that Dr. Brazil's method of producing specific antivenomous serums in fluid form for the bites of different types of poisonous snakes is the radically successful method of snake-bite treatment."

Finally, an antitoxin which I succeeded in preparing at Butantan with *C. atrox* venom sent to me by Dr. Ditmars in 1919 from the Zoological Garden likewise showed some strength in checking the experimental poisoning by *C. terrificus*, determined either *in vitro* or *in vivo*. Cures of people bitten by "copper-head" and injected with Brazilian antitoxin have been reported in this country, and can be explained in the same way, that is, by this paraspecific action.

ACCIDENT TREATMENT

When a snake bite occurs, the first thing we do in Brazil is to discover the type of poisoning, either by seizing the snake or by carefully observing the symptoms. The differentiation of type of poisoning is quite easy in countries such as mine, where this study has been undertaken for many years.

When the species is recognized, we inject a specific monovalent antitoxin; when, however, we are in doubt, we inject a polyvalent antitoxin, which, though weaker than a monovalent one, is active enough to suppress many of the toxic phenomena.

For this reason, and also because of our having sometimes to deal with many different species of snakes, the Institute de Butantan has prepared six kinds of venom antitoxins:

1. Anti-Crotalic monovalent antitoxin, for *C. terrificus* bites.
2. Anti-Bothopic monovalent antitoxin, for *B. jararaca* bites.
3. Anti-Bothopic polyvalent antitoxin, for *B. jararaca*, *B. jararacussi*, *B. atrox*, *B. alternatan*, and *B. neeviedii* bites.
4. Anti-Elapinic polyvalent antitoxin, for *Micrurus* (*Elaps*) *frontalis*, *Micrurus corallinus* bites (Coral snakes).
5. Anti-Ophidic polyvalent antitoxin, for every kind of snake bite. It is used when the snake has not been seen and the type of poisoning has not been recognized.
6. (North American) Crotalic antitoxin, for *C. atrox* bites.

Doses and Channels

Whatever the time of the accident, an initial dose of about 20 c.c. is injected subcutaneously into the arm or between the shoulder-blades. In severe cases the injection is given intravenously. If the symptoms do not recede, or, on the contrary, relapse, a second injection of 20 c.c. or even 40 c.c. is given. Local injections are reserved for cases in which the swelling, edema, ecchymosis or other local symptoms are very marked.

The earlier this treatment is used the more frequently it succeeds. It is effective within the first twenty-four hours after the accident. This time is usually sufficient for a person in my country to procure the antitoxin if he does not have it at home.

Discussion:

DR. ROHDENBURG: I should like to ask what your impression has been in Brazil regarding the use of alcohol after snake bites. Is there any reason for giving people alcohol after they have received a snake bite?

DR. AMARAL: Alcohol helps the poison. When a person is bitten by a venomous snake and alcohol is taken, the poison is much more severe, for alcohol facilitates the penetration and absorption of the venom.

DR. ROHDENBURG: About how much rattlesnake venom will kill a man?

DR. AMARAL: About sixty milligrams, that is, one milligram per kilo of body weight.

DR. PLAUE: In South America, is it helpful, if one has courage enough, to cut out the surrounding skin and muscle in the region bitten by the snake? There is an old story that if the surrounding tissues are cut out the patient will get well.

DR. AMARAL: Sometimes that will happen if it is done within one, two, or five minutes after the bite has occurred, but it does not succeed later, because the venom penetrates very quickly. When local treatment, such as scarification, ligature, application of fire, and so forth, are made a few minutes after the bite, they do succeed. In general, people do not use them in time.

DR. CORNWALL: Assuming that a lethal dose of venom has been received, about how soon is it necessary to give the serum to prevent a fatal issue?

DR. AMARAL: That depends upon the type of poison. In general, serum is advisable within twenty-four hours after the bite has taken place, because death usually occurs after the twenty-fourth hour. In very exceptional cases, death can occur before this time, namely, in case the venom is injected into a vein, but this is exceptional, and I never observed such a case myself.

DR. PAPPENHEIMER: In the cases in which the gangrene of all the soft parts occurs, is that due to edema and shutting-off of the blood supply, or to direct toxic necrosis?

DR. AMARAL: When gangrene occurs, it is due to the local action of the venom, that is, the proteolytic substances in the venom. Venom is a very complex substance; it has hemolytic, cytolytic, neurolytic, and other activities. In the case of a rattlesnake bite, the symptoms are nervous; we get paralysis, and so on. In the case of the coral snake bite we have lacrimation, paralysis, etc.; in the case of the copperhead, necrosis and gangrene. With the diamond-back rattlesnakes there occurs gangrene, swelling, edema, ecchymoses, and so on. With snake bite we have not only local symptoms, but also generalized symptoms, the nose, skin, eyes, and so forth, being affected in very severe cases. But when the infection is due to the bite, antitoxin neutralizes the action of the active principles of the venom, and it is active against every kind of toxic principle of the venom.

DR. MOENCH: Does the fact that death usually takes place only after twenty-four hours or more apply to all venomous American snakes? Does not death usually occur within two or three hours after a cobra bite?

DR. AMARAL: Yes, the time of death varies according to the species of snake. In the case of the cobra bite the venom is hemolytic and neurolytic at the same time, and so very severe nervous symptoms occur after such a bite. After a cobra bite the serum should be injected within the first hour, but in the case of a rattlesnake bite, we can inject the serum after ten or twenty hours, and usually succeed. Cobra venom is very hemolytic.

DR. VERNICKE: Is there any natural immunity against snake bites?

DR. AMARAL: No, there is none. The attempt to produce active immunity is not advisable, because the injection of venom into a man is a serious pro-

cedure, and it has a definite action on the liver. People in Africa were sometimes injected with venom, with at times fatal results. Our horses, after three or five years of use, often die of rupture of the liver. The venom produces an amyloid and fatty degeneration of the liver, and sometimes, if the venom is not very carefully weighed, it can produce a paralysis. Immunization of man is not possible. Natural immunity is found in some animals who have acquired the habit of feeding on snakes. The animal I showed in one of the slides is very definitely immune against snake venom. We have two species of the same kind, a Northern and a Southern species, the former, which has acquired the habit of feeding on snakes, is immune, but the Southern species is not immune at all. It has not acquired the habit of feeding on snakes. The Northern species only has acquired immunity.

DR. PLAUT: Do only horses which have been treated with snake venom die of rupture of the liver, or can you see the same thing in horses which have been treated with other injections? I ask for this reason; horses which are used in making diphtheria antitoxin also acquire amyloidosis of the liver.

DR. AMARAL: I have also seen death in horses immunized against diphtheria. But in the case of snake venom, death is quicker. We know the liver has a very antitoxic property. The liver neutralizes venoms. I never saw a case of rupture of the liver in horses immunized against tetanus toxin, which has no action on the liver.

DR. VANDER SMISSEN: Has anyone tried to make a serum from the animal which is immune, and see whether that could be used for immunization?

DR. AMARAL: I tried the serum, but it could not be used in immunization, because the animal is not very common.

DR. MOENCH: I do not know whether it is true or not, but I have been told by friends who had lived in India that they got rid of cobras there by using pigs which fed on these snakes without apparent harm. As I understand it, the pig is not itself immune to snake bites, although it usually escapes. Furthermore, there is a report in many of the books on explorations that certain of the African tribes have a strong immunity to snake bites, which they get by eating the poison-sacs of these snakes. It interested me especially in this connection to learn that the Northern skunk-like animals in South America who feed on snakes are immune, while the Southern animals of the same species who do not eat snakes are not. Do you know anything specific about these immunity stories?

DR. AMARAL: The pig is not immune against snake venom. When the snake bites the pig, the pig does not always die because it does not absorb the venom, the venom being injected into the subcutaneous fat and not absorbed. But when a cobra or another snake bites the pig in the mouth or in the foot the pig does die, for in these localities there is quick absorption. He is not immune. In Martinique Island they introduced the mongoose to kill snakes, and they succeeded in extinguishing them, but the country is very small. In a big country you could not use the same plan. The question as to whether immunity

appears after the absorption of venom by the intestinal tract can be answered by saying that it is not at all possible because the toxin is destroyed in the stomach and does not pass into the circulation. The immunity of the animals that I showed is easily explained in the following way: Some of them before being immune got the habit of feeding on snakes because they did not find another kind of food, and they had the good fortune to meet a snake which did not have a big quantity of venom, and thus a little venom was injected, not large enough to kill the animal, but large enough to begin immunity. After the second, third, or fourth bite the animal became immune, and after many generations it has kept the immune property. I believe it is true that you can not explain every natural phenomenon, but I think that this is the possible explanation in this instance.

DR. VANDER SMISSEN: Would you advise the use of alcohol after the poison has been spread through the body and there is definite heart weakness? Do you think it would do any harm?

DR. AMARAL: Alcohol must not be used in any condition. In every country we know that there are people who claim that their medicines are very powerful against snake bites, and these medicines are usually alcohol with some botanical principle. I use the following experiment to show the effect of alcohol: Dog I received one minimum lethal dose of venom. Dog II received the same amount of venom plus alcohol. I observed the following: The first dog died in twelve, and the second dog within eight to ten hours. I never observed an exception to this. Alcohol facilitates the absorption of the venom through the body. In another experiment we used Dog III, who received a minimum lethal dose of *Bothrops jararaca*, the control dog received the same kind and the same amount of venom, with alcohol. The first dog died after twenty hours, and the second dog after fourteen hours. In every case, with every kind of venom, it is shown that alcohol facilitates the absorption of the venom.

CASES ILLUSTRATING THE RELATION OF SUP- PURATIVE PHLEBITIS TO SEPTICEMIA

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The subject of this brief presentation is hardly a novel one. One hundred and twenty years ago, John Hunter published in the *Proceedings of the Society for Medical Improvement* his *Observations on the Inflammation of the Internal Coats of Veins* from which I should like to quote a few paragraphs:

" . . . the inside of veins, as well as of all other cavities, is a seat of inflammation and abscess. I have found in all violent inflammations of the cel-

lular membrane, whether spontaneous or in consequence of accident, as in compound fractures, or of surgical operation or in the removal of an extremity, that the coats of the larger veins, passing through the inflamed part, become also considerably inflamed, and that their inner surfaces take on the adhesive, suppurative, and ulcerative inflammation, for in such inflammation I have found in many of the veins adhesions (thrombi?), in others matter, and in others, ulceration. Under such circumstances, the veins would have abscesses in them, if the matter did not find in many cases an easy passage to the heart along with the circulating blood, so as to prevent the accumulation of pus; but this ready passage of the matter into the common circulation does not always happen. It is in some cases prevented by the adhesive inflammation taking place in the vein between the place of suppuration and the heart, so that an abscess is formed, etc."

It is clear from this and other passages in the article quoted that Hunter appreciated, as well as one could before the days of bacteriology, the importance of infection of the veins as distributing centers for generalized infection. It would seem that such suppurative inflammation of the veins, leading to fatal sepsis, was a not infrequent sequel to phlebotomy. It is of course universally recognized that suppurative inflammation of the uterine and ovarian veins in puerperal sepsis, and of the jugular vein and lateral sinus in otitic disease, leads almost inevitably to bacteriemia and generalized infection.

The war furnished us with many other impressive examples of this association. Among the 230 autopsies performed at the Presbyterian Base Hospital, there are records of twenty-four cases of septic infection of the veins complicating infected wounds of the extremities, often with compound fractures, in fourteen instances necessitating amputation. In six of these cases, no blood cultures were taken; of the remaining eighteen, fourteen yielded streptococci, one case *Staphylococcus albus*; only three were sterile. So far as our records go, every case showing a positive blood culture and ending fatally proved at autopsy to have had an infection of the veins.

We had thought that these war wounds, attended as they were with extensive injury to bones, soft parts and vessels, constituted rather a special group of cases. But the following examples, chosen from recent hospital protocols, which I shall present only in briefest outline, will serve to show that in civil life also, infec-

tion of the veins is a most important—probably the most important—factor in the generalization of streptococcal or staphylococcal infection.

The gross findings in this group of cases are repeated with but slight variations. The affected veins are opaque and indurated, but not necessarily greatly distended or enlarged. They are often adherent to adjacent structures. When they are dissected out and opened, the lumen, in the region of maximal infection and for a varying stretch above and below it, is found filled with thick fluid pus, smears from which invariably show numberless organisms. When the purulent exudate is removed, the wall is seen to be lined with a rough necrotic adherent slough or exudate; or with a more delicate fibrinous membrane; or if the process has lasted a sufficient time, with a velvety layer of granulation tissue.

As one ascends from this area in which the vein is filled with fluid pus, the contents change gradually into friable grayish-red thrombus, completely occluding the vessel; and at the upper extremity the thrombus is rounded, unless an embolus has been broken off. In the numerous cases in which the infection has arisen in one of the veins of the lower extremity, the thrombus is found extending into the inferior cava for a distance of several inches, often straddling the bifurcation and reaching a variable distance into the common iliac on the opposite side.

The histological study of numerous sections from these cases has led us to the following conception of the process. The infection probably starts in one or more of the small tributary veins in the infected focus. The bacteria grow upward along the inner surface of the vessel, carried on perhaps by the still circulating blood. Wherever they gain lodgment, there is produced a necrosis of the endothelium and of the underlying intimal tissue, and an inflammatory reaction in which the elements of the vein itself play a leading part. There is at first a polymorphonuclear leucocytic response; the leucocytes wander from the adventitia through the muscular coat and form a dense layer beneath the necrotic zone. Sometimes they appear to be partially arrested by the still intact elastica interna beneath which they ac-

accumulate, forming at times veritable pustules. With this cellular emigration, there is also an exudation of fibrin between the muscle fibers and also upon the internal surface, where the fibrin often has a lamellar arrangement and forms a typical diphtheritic membrane.

Quite early in the process, there occurs a proliferation of the fixed elements. Fibroblasts and angioblasts grow inward through the media at right angles to the circular muscle fibers, penetrate the internal elastic membrane or push it up from the media, and eventually organize more or less completely the necrotic exudate or fibrinous membrane. Many large and small mononuclears accompany the connective tissue and blood vessels in the later stages of the process.

Blocks taken through the upper portion at a distance from the site of intense inflammation show typical thrombi in various stages of organization, depending upon the length of time that the infection has lasted. The inflammatory reaction in the vessel wall itself becomes correspondingly less intense, and near the summit of the thrombus, the vessel wall resumes its normal structure. Distal to the suppurative area, the veins are filled for a varying distance with propagated clot which also may become organized.

There are many interesting details which cannot be discussed within the limits of this paper. I may however state our main conclusions. We have been led to the opinion that the infection of the veins is comparable in every respect to the bacterial infection of other serous membranes, such as the endocardium or peritoneum. The thrombosis is a secondary phenomenon, which does not take place at all in these segments of the vein where the inflammation is most intense, but in areas above where the bacteria are presumably less concentrated and the inflammatory reaction less intense. The inflammatory exudate which fills the vein is derived, not from the softening of pre-existent thrombus, but from the *vasæ vasorum* and the new formed vessels which invade media and intima from without. The bacteria remain localized to the inner surface of the vessel. We are of the opinion, finally, that generalization of a streptococcal infection is

usually, and perhaps always, associated with a suppurative infection of regional veins about an inflammatory focus.

ILLUSTRATIVE CASES

Autopsy 8923. The patient, a boy eight years old, gave a history of an infected scratch on the left foot for five weeks before death. One week after injury, the onset of symptoms of acute infection occurred, with pain in the left knee and thigh. Operation revealed suppurative periostitis of left femur. *Staphylococcus* was obtained from blood and pus. Sepsis was continuous, and death occurred four weeks after operation. Autopsy showed the following lesions: osteomyelitis and suppurative periostitis of left femur; suppurative phlebitis of left femoral vein; suppurative pericarditis; abscesses in myocardium, lungs, kidneys and skin, etc.

9177. The patient, a boy thirteen years old, had a history of furunculosis, the last furuncle having been in the left ear one month previous. He entered the hospital in a stuporous condition, intensely septic. The left thigh was swollen from the hip to the knee. Hemolytic *staphylococcus* was recovered in the blood. An operation for osteomyelitis of the left femur was performed, with continued sepsis. Death occurred six days after admission to the hospital, and twelve days after the onset of the symptoms. Autopsy showed osteomyelitis of left femur; suppurative phlebitis of left femoral vein; tricuspid endocarditis, *staphylococcus*; and pulmonary infarction.

9201. A woman, aged fifty-seven, had an infection of the right thumb ten days before admission. This was incised. A scratch on the right leg was followed by cellulitis. On admission the temperature was 104. There was cellulitis of the right leg and thumb. The blood culture showed *Staphylococcus aureus*. Thrombosis of the right saphenous vein occurred. The vein was ligated. Sepsis continued; death intervened nineteen days after infection began. Autopsy showed abscess of thumb; abscesses of lungs and kidneys; suppurative phlebitis, internal saphenous veins; varicose veins of legs, with thrombosis.

9372. A woman, aged thirty-eight, had an infection of the left knee four and a half weeks previous to admission, with symptoms of general sepsis for two weeks. There was marked cellulitis of the left thigh with evident venous thrombosis. Hemolytic streptococci were recovered from the blood. A portion of the internal saphenous vein was excised. There were continuous positive blood cultures. Death occurred seven weeks after the onset of the initial infection. Autopsy showed cellulitis of thigh; suppurative phlebitis of saphenous, femoral, and external iliac veins; acute aortic endocarditis; infarcts of spleen and kidneys; acute glomerulonephritis.

9361. A woman, forty-six years old, had an abscess of the left thigh of two weeks' duration, with intense sepsis. The abscess was incised and drained, with continuance of septic symptoms. Hemolytic streptococci were recovered in the blood, and death occurred six and a half weeks after the onset. Autopsy showed abscess of left thigh; suppurative phlebitis of the left femoral vein.

Discussion:

DR. PLAUT: I understood from Dr. Pappenheimer's conclusions that he considers it is not thrombosis but endophlebitis which is the real character of the changes in the veins leading to septicemia. I would like to ask if he has not seen cases of general septicemia where only the first stage was to be found in the infected vein, where there was no thrombus in the vein, but only the endophlebitis. I remember several cases without any thrombus in the vein, which was the origin of the pyemia, and in cases also after tonsillitis with necrosing endophlebitis in the small veins going to the internal jugular, and after abortion in the small veins of the pelvis. There was no thrombus at all, but a dark greenish change in the intima of the vein at this point.

DR. WOOD: I have seen an interesting case clinically in which there was no thrombosis and no final septicemia. The patient recovered perfectly, although the whole saphenous vein was thickened and cord-like. The reason we knew there was no thrombosis was because the surgeon happened to take out most of the vein and submitted it to me for examination. It was largely a mural infection with an unidentified organism, not a staphylococcus. The vein was perfectly patent except for the thickening of the wall and occasional patches of fibrin on the inside, but it never went on to the stage of complete thrombosis.

DR. PAPPENHEIMER: I can not say I have seen any case in which there was no thrombus at all, but I have seen cases in which the thrombus was parietal and did not completely occlude the vessel, but in this series all showed at the upper extremity more or less definite thrombus formation. I am sure there are cases such as have been described, but I have not seen them myself.

RUPTURED PAPILLARY MUSCLE OF THE HEART REPORT OF A CASE

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Rupture of the papillary muscle of the heart is such an unusual occurrence that it deserves especial mention.

The patient was a white woman, sixty-nine years of age (History 54158, Autopsy 9250), who was admitted to the Medical Service of the Presbyterian Hospital on May 22, 1922, complaining of weakness of six days' duration. Her family history and past history were negative. Her illness began on May 16, when, while ironing, she suddenly became very weak, with a sense of oppression in her chest and a choking feeling. She perspired freely, felt as if she were going to faint, but did not lose consciousness. Since the onset general

weakness has been persistent. The physical examination showed slight cyanosis of the lips, irregular pupils; veins of the neck full. The apex impulse of the heart was in the fifth space 10 cm. to left of the midsternal line; the left border was 13 cm. to the left, and the right border was 4 cm. to the right of

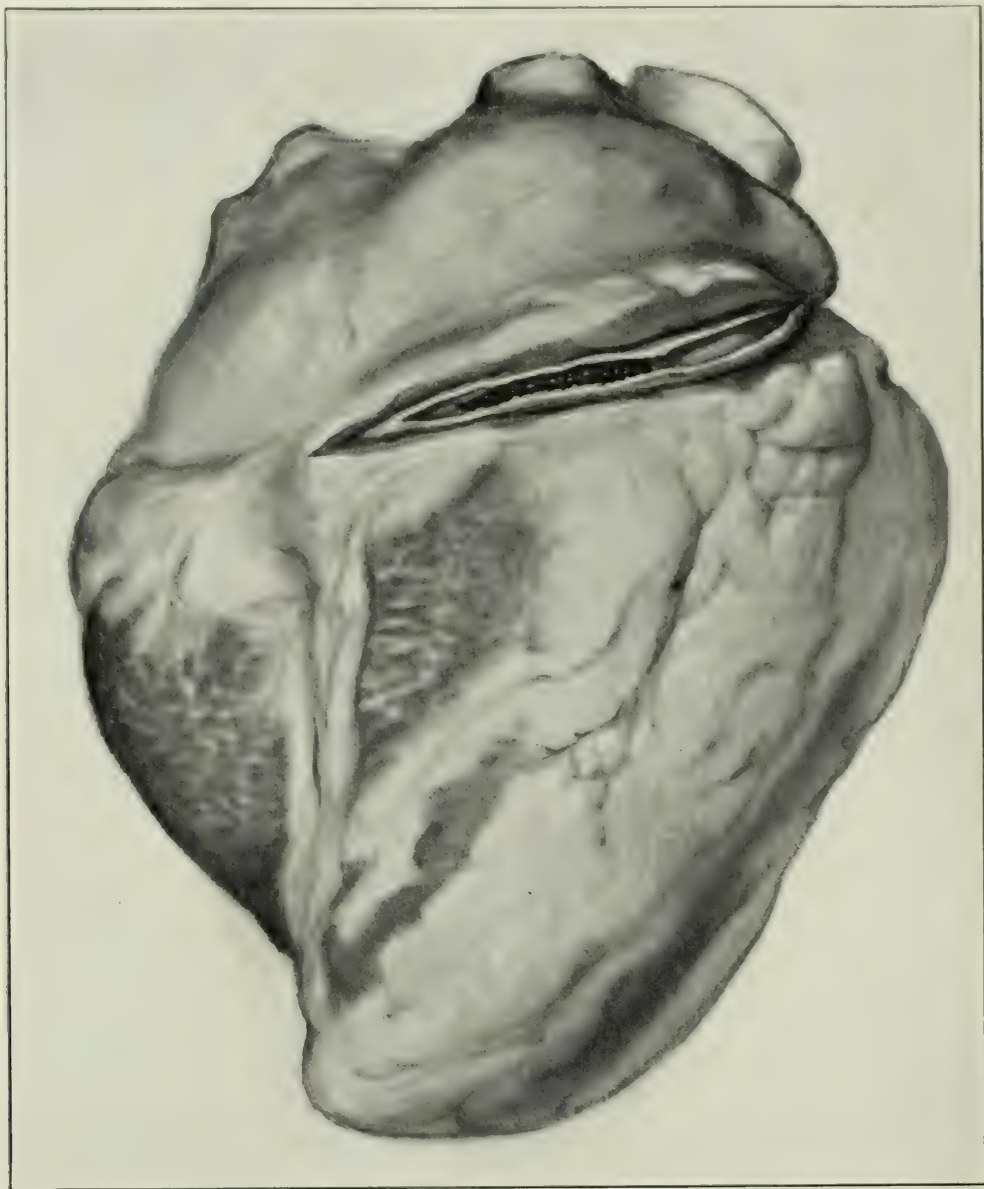


FIG. 1. (Autopsy 9250.) Sclerosis of right coronary artery with calcification and thrombus formation. Healing infarcts of right and left ventricles.

the midsternal line. The heart sounds were faint and of poor quality; there was a high pitched systolic murmur heard all over the precordium and in the left axilla. The action of the heart was rapid and absolutely irregular. There was no pulse deficit. The blood pressure was systolic, 100; diastolic, 70. The

electrocardiogram showed sinus arrhythmia with a possible shifting of auricular pacemaker. Later electrocardiograms showed premature contractions of unknown origin, auricular tachycardia, with striking form or rhythm changes in almost every record. She was given quinidine, and under this therapy the pulse became regular though she still had dyspnea and cyanosis. On June 1st, she developed a left hemiplegia and facial paralysis. On the following day the dyspnea and cyanosis were more marked, and there was definite increasing heart failure. The blood pressure had risen to systolic, 135; diastolic, 90. She died on June 6.

The organ of interest at autopsy is the heart which weighs 320 gm. The posterior part of both right and left ventricles feels rather softer and flabbier than usual, and the myocardium in this portion has a sunken appearance. It is dark red in color, with reddish-yellow bands passing across it. The epicardium in this region is smooth. The myocardium of the right ventricle close to the septum and extending downward from the auriculo-ventricular groove has lost its usual appearance and is dark red in color. The muscle fibers seem shrunken and there is a little bloody fluid between them. The wall of the left ventricle opposite this is distinctly thinned out; it is dark red in color, and there is also some bloody fluid in this portion. This thinning with obvious infarction extends over beyond the point of origin of the posterior papillary muscle. This papillary muscle arises by two distinct pillars which join together not far from the point of origin, but later separate forming an X-shaped mass. The distal portion of these two masses is united by two tendinous bands resembling chordæ tendineæ. The portion of the papillary muscle nearest the septum is shrunken, and beneath the endocardium the muscle appears yellowish and opaque. This necrotic muscle is sharply marked off by a distinct line of demarcation at the point of origin of the muscle. At a point one cm. from the origin, the muscle is ruptured transversely in a slightly oblique direction. The ruptured ends of the muscle are covered by a thin thrombus. The distal portion of the ruptured muscle is held roughly in position by the two tendinous bands which united this half of the papillary muscle to the other half. The unruptured half of the papillary muscle is thinner than the normal and shows infarction. The myocardium in other parts of the ventricle is slightly brownish-red in color, with some increase in connective tissue. The valves of the heart are negative except for early sclerosis at the base of the aortic leaflets. In the left coronary artery there are numerous yellow plaques of sclerosis without calcification. They, however, encroach on the lumen. The right coronary contains numerous sclerotic plaques, and at a point 4 cm. from the orifice there is a large plaque with some calcium in it. At this point there is a thrombus occluding the vessel for a distance of 2 cm.

The sections of the papillary muscle show complete disappearance of the nuclei of the muscle cells, with swelling of the fibers and loss of striation. In between the muscle fibers there remain some of the endothelial cells lining the vessels and connective tissue cells, but for the most part only the shadowy outlines of cells and nuclear debris are found. The surface of the muscle is covered with thickened edematous endocardium, and on the endocardium is a thin thrombotic mass. The torn end of the muscle is covered with a thrombus

of recent formation. In other parts of the myocardium there are rather dense avascular scars and more recent vascular scars. There is also a recent infarct with some hemorrhage.

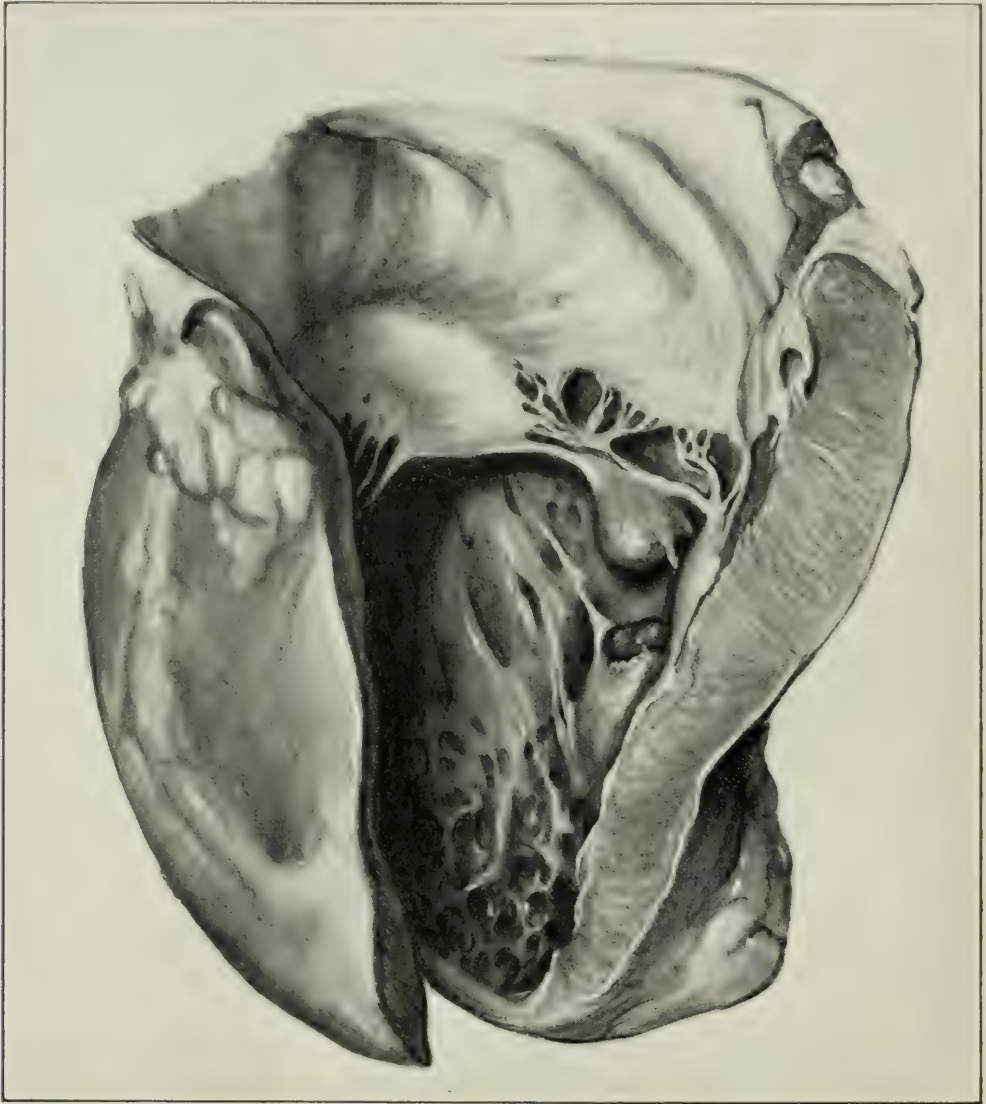


FIG. 2. Rupture of posterior papillary muscle of left ventricle, following infarction

There are on record only eight other cases of rupture of the papillary muscle and in all these the ruptured muscle has been located in the left ventricle. Wankel in 1911 reported one case, and in a search of the literature found only four others. Teacher in the same year reported a case. In four of these six cases there was sclerosis of the coronary arteries, and in two there was

thrombosis of these vessels. In one case no mention was made of the condition of the coronaries, and in one case they were reported as being negative. In a case reported by Spalding and VonGlahn, there were demonstrated spirochetes in the ruptured papillary muscle. Recently a case of rupture of the papillary muscle associated with sclerosis of the coronaries has been reported by Fisher; in this case the patient lived ten months. In the case reported here there is infarction of the right and left ventricles, with infarction and rupture of the posterior papillary muscle of the left ventricle, following sclerosis of the coronary arteries with thrombosis of the right coronary artery.

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CORONARY DISEASE AND INFARCT OF THE HEART

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The pathological conditions affecting the width of the lumen of the coronary arteries may be conveniently grouped according as they arise in adjacent structures and secondarily involve the vessels; second, pathological conditions occurring in the vessels themselves, and last, the occlusions resulting from embolism. In the series of cases reported here, I have included only those conditions in which there were either complete occlusion of one of these vessels or reduction of the lumen to such an extent that it was a practical occlusion. There have been thirty-six such cases found in the last 1600 autopsies performed at this institution.

*1. Occlusion of the Coronaries Resulting from Conditions
Arising Principally Outside of the Vessels*

In this group are not included those conditions of advanced sclerosis of the aorta with constriction of the orifices of the coronary arteries, as usually in that condition the coronary arteries themselves are so extensively involved that they have been included in the second group. There are two examples of occlusion of the coronary artery resulting from changes beginning outside of these vessels, and these have been associated with syphilitic aortitis. In each of these instances, the orifice of the right coronary artery has been entirely occluded, apparently by the extension of the process from the aorta into them. In each of these cases, the orifice of the coronary artery is at a higher level than normal, and it would seem that this anomalous origin plays an important rôle in the occlusion of the vessel by the syphilitic process in the aorta.

It will be recalled that the syphilitic process in the aorta usually ends at the upper level of the sinus of Valsalva, or occasionally it may extend downward along the attachment of the valves. In attempting to determine the normal origin of the coronary arteries, considerable difficulty was encountered in ascertaining the upper level of the normal site of origin. It is stated that the coronary arteries arise in the sinus of Valsalva at or below a point level with the free margin of the valve. As the level of the free margin of the valve is a little below the level of the highest attachment of the valve, it has been assumed that any origin of the coronary arteries above the level of the highest point of attachment of the aortic cusps constitutes an anomalous position.

With this as a standard, each case of syphilitic aortitis in our records has been reviewed, and it has been found that in the sixty-five cases, in addition to the two complete occlusions, there were six in which the orifice of one or both of the coronary arteries was encroached upon. In five of these six, the involved artery arose well above the point of highest attachment of the valve. In the other instance the involved vessel came off on a level with this line.

The question arises whether the orifices of the coronary arteries can be pulled upward by the scarring occurring in the wall of the aorta in an advanced syphilitic aortitis. This would appear to be very improbable, for it does not seem likely that the orifices of the coronary arteries can be pulled upward without a similar distortion of the lower margin of the valve, which has not been observed in any of these cases; neither does it seem likely that the orifice of the involved artery could be pulled upward and the highest point of attachment of the valve be left undisturbed, and finally, in some of the cases one artery arose normally while the other artery was in an abnormally high position. The relationship of these various arteries to the aortic valves is shown in Figure 1.

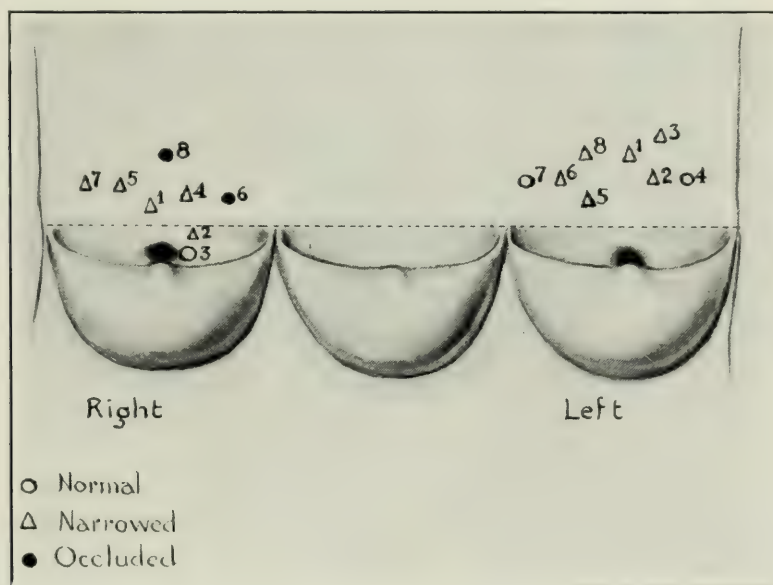


FIG. 1. Diagram showing normal origin of the coronary arteries, and the position of the orifices of the coronary arteries involved in syphilitic aortitis. Distance in millimeters from the dotted line. Arteries from each case indicated by the same numeral.

It would seem, therefore, that the anomalous origin of the coronary arteries is the important factor in the involvement of the orifices of these arteries in syphilitic aortitis.

In one case of complete occlusion of the orifice of the coronary artery there were symptoms of angina pectoris. In neither

of these cases, where there was complete occlusion of the orifice of the coronary artery, was there infarction of the heart. This is probably accounted for by the fact that the other vessel was normal, or the occlusion was slow and the collateral circulation was sufficiently established.

2. Occlusions Due to Changes within the Vessel Itself

This constitutes the greater number of cases in this series; there were thirty-three of this type. Of these cases, twenty were males, thirteen females; and twenty-six occurred between the fifth and seventh decades. The changes in these vessels consist of arteriosclerosis, generally with the deposition of a considerable amount of calcium, with constriction of the lumen, and at times with the formation of a thrombus at the point of narrowing. In studying the extent of the calcification of the vessels, we have found that x-ray of the heart after removal gives an excellent idea of the vessel involvement (Figure 2). In seventeen cases thrombi were found. The right coronary artery was thrombosed three times, and the left fourteen. In two cases both the right and left vessels were thrombosed.

Of these thirty-three cases, the left coronary artery was occluded twenty-six times. In five cases, the records state that only the left vessel was the site of occlusion. In fourteen, the anterior descending branch of the left coronary has been the site of an occlusion; the circumflex branch of the left was involved seven times, and both the circumflex and descending branches once. The right coronary artery was occluded four times. It is seen, therefore, that the left coronary artery is much more frequently involved than the right, and that the anterior descending branch of the left is the vessel most frequently involved.

The changes which result from these occlusions may be variable. There may be simple atrophy of one portion of the heart wall, as in one instance where the posterior wall of the left ventricle was only about one half the width of the anterior wall, and x-ray of this heart revealed the circumflex branch of the left coronary artery to be markedly calcified. Usually, however, there is scarring or infarction. There were three recent and one

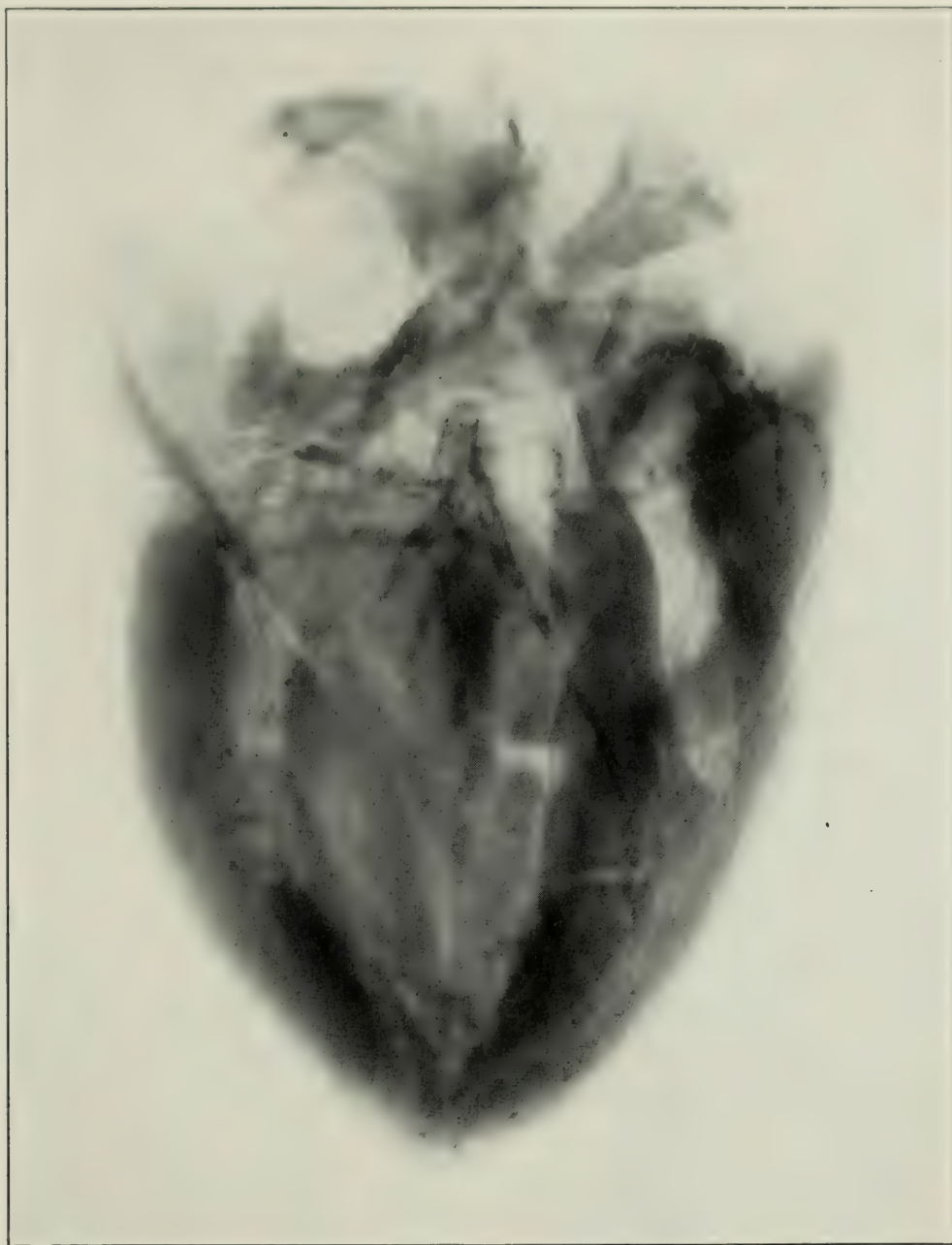


FIG. 2. X-ray of heart: Extreme calcification of the coronary arteries (Autopsy 9112)

old infarct in the right ventricle, and in the left ventricle there were ten recent and fifteen old infarcts. Rupture of the heart as a result of infarction occurred twice, once each in the right and left ventricles. Rupture of a papillary muscle occurred once.¹

¹ Von Glahn and Horowitz: *Proc. New York Path. Soc.*, 1923, xxiii, 103.

In an analysis of the clinical symptoms of these patients, it is found that in eight cases only were there definite anginal attacks. These lasted from one week to twenty years. The majority of these patients complained of precordial pain.

3. Occlusion Resulting from Embolism

There is only one example of an embolus in the coronary artery. In this instance there was a pedunculated vegetation on one of the leaflets of the aortic valve, and this vegetation was swept into the left coronary artery.

SUMMARY

1. In those conditions in which syphilis is the etiological agent in the occlusion of the orifices of the coronary arteries, the abnormal origin of the coronary artery appears to be an important predisposing factor in their occlusion.

2. The majority of occlusions of the coronary arteries result from arteriosclerosis, usually with calcification, and frequently with the formation of thrombi.

3. Embolism of the coronary artery is of infrequent occurrence.

4. Following the occlusion of the coronary artery, there may be no change in the myocardium, or there may be atrophy of a portion of the heart wall, diffuse scarring, or the formation of infarcts. Rupture of the heart or papillary muscle is an infrequent complication following infarction.

CASES ILLUSTRATING MALIGNANT TUMORS OF
LUNG AND PLEURA *

WILLIAM C. VON GLAHN, M.D.

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Columbia University, New York)

Within the last two years, there have come under our observation six cases of primary tumor of the lung and pleura. To this group I have been privileged to add two cases which came under my observation in the City Hospital at Baltimore, Maryland, making in all eight cases to be reported here. These tumors may be conveniently grouped in the following manner: First, those arising from a primary bronchus, or the main bronchi, to one of the lobes of the lung; second, tumors arising from alveolar epithelium; third, tumors arising in tuberculous lungs; fourth, tumors arising in bronchiectatic cavities, and finally, a tumor of the pleura.

1. Carcinoma Arising from Primary Bronchi

There are three examples of this type.

Case 1. A man, aged fifty-one years, complained of fever for five weeks. The onset was two years ago with chronic bronchitis and asthma. A year ago he was sick for three weeks, presumably with pneumonia. Following this, his asthma became worse, and he had dyspnea on exertion. Bronchoscopic examination was negative, but following it he raised a considerable amount of foul sputum with relief.

The physical examination, aside from revealing dullness over the right upper lobe, was negative. The x-ray showed a dense shadow at the right base, suggesting fluid, and fluid was obtained by aspiration. Later a rib resection was done, with drainage of this pleural cavity.

The autopsy (No. 9238) revealed a collapsed but rather dense right lung, with numerous adhesions binding the three lobes together, and the surface was covered with a thick fibrino-purulent exudate. The lung was everywhere adherent to the mediastinum except along the upper lobe. The trachea in its upper half appeared quite normal. About 3 cm. above the bifurcation, the mucous surface of the trachea was roughened by numerous small rounded

* Abstract of paper read before the N. Y. Pathological Society; to be reported in detail elsewhere.

elevations, which extended down into the primary bronchus for a distance of 2 cm. on the left, while in the primary bronchus on the right these small nodules were found to extend into the bronchi of the three lobes. The lumen of the right primary bronchus was markedly narrowed by the thickening of its wall just before it divided into its three main branches, and the bronchi to the upper and middle lobes were so constricted that only the finest probe could be passed through them. These bronchi contained a considerable quantity of purulent material, and in the lower lobe there were numerous small cavities containing pus, into which some of the bronchi very definitely opened. In many places throughout the lung there were areas of consolidation. The left lung was negative except for the involvement of the primary bronchus. At the hilum of the right lung there were some lymph glands tightly adherent both to the bronchus and to the esophagus. These glands contained a considerable amount of gray translucent tissue, obviously new growth.

The histological examination revealed a tumor composed of large cells replacing the mucosa of the primary bronchus. These cells have rounded or oval, vesicular nuclei, often with a large nucleolus. The tumor is extensively infiltrating the submucosa and is found lying in the lymphatics outside the cartilaginous rings of the bronchus. In other parts the tumor cells are smaller; they stain more intensely with the basic dyes, and in between many of these cells there is a mucin-like substance. In the right lung the lymphatics are frequently found hugely distended by solid masses of tumor with only occasional production of mucin. Within these masses of tumor are found many irregular nodules of calcium. In addition to this there are found many infected bronchiectatic cavities. In the hilar lymph glands are found large masses of tumor having a somewhat adenomatous arrangement, with mucin. In other of the glands the cells are growing in rather solid masses, as seen in the lymphatics. There were no other metastases demonstrable.

Case 2. A white man, seventy-five years old, complained of pain and distress in the right chest. His history was very inaccurate, the duration of illness being given from two years to one month.

Physical examination revealed dullness in the right axilla, flatness at the right base posteriorly and absence of breath sounds. X-ray showed dullness over the right lung, with increasing density toward the base. A diagnosis of primary neoplasm of the pleura was made.

At autopsy (No. 9261), the right pleural cavity was found to contain 600 c.c. of blood-tinged fluid. The parietal pleura was studded and thickened by nodules and flat plaques of gray translucent tissue which was very dense and firm. The thickening was particularly marked over the apex of the right lung, where the width of the pleura was almost 1 cm. In the lower lobe at the end of the main bronchus there was found a large mass along the mesial border, measuring almost 6 cm. in its greatest diameter. This mass was composed of opaque yellow tissue in which were pockets filled with pus. The pleura directly over this was thickened and pulled in. The bronchus leading to this mass was constricted, and the wall infiltrated by tumor. The lymph glands at the hilum of the lung contained many tumor nodules.

This tumor is composed of oval or polyhedral cells forming large masses; in many places these cells are definitely flattened and squamous-like. The

nuclei are vesicular and oval, containing little chromatin. Mitoses are numerous, and in some areas there is keratinization without definite pearl formation. The tumor is extending from one alveolus to another through the pores of Cohn. In some places the alveolar septa have been destroyed. There is extensive necrosis of the tumor in many parts. In some of the bronchi the mucosa has been replaced by tumor. The lymphatics are extensively invaded; in a few instances plugs of tumor are found in the smaller branches of the pulmonary artery. Metastases are found in the pleura, lymph glands, and kidney. There is no mucin production in this tumor.

*Case 3.*¹ A man aged forty-seven years, complained of epigastric pain, nausea, and vomiting. The history was very suggestive of gastric ulcer, for which he had been previously treated.

On physical examination there was found dullness over the right apex, with a change in breath sounds. X-ray of the chest revealed a dense shadow in the right upper lobe, with displacement of the trachea to the right, and with an apparent pulling upward of the primary bronchus. A bronchoscopic examination showed the main bronchus to the right upper lobe reduced to a small slit from which pus exuded.

At autopsy (No. 9379), the right upper lobe was bound to the parietal pleura by dense adhesions. The bronchus to this lobe was filled and distended by a plug of soft gray tissue. This tissue passed through the wall of the bronchus and extended into the surrounding lung and pleura. The mass extended backward into the bronchus for a distance of 2.5 cm., and beyond this point in the upper lobe there were numerous bronchiectatic cavities filled with pus. A small branch of the pulmonary artery passing close to the tumor was found to be invaded by the tumor. The lymph glands at the bifurcation of the trachea and about the right primary bronchus were greatly infiltrated with the tumor. Other additional findings at autopsy were a small gastric ulcer, a duodenal ulcer, a scar in the right lobe of the liver, congenital cystic kidneys, with numerous adenomata, and a necrotic mass in the right lobe of the cerebellum.

The histological examination showed the tumor in the region of the primary bronchus to be composed of cells having spindle-shaped, vesicular nuclei, and very scant cytoplasm. These cells have a definite alveolar arrangement: the stroma seems to be very scanty. They are invading between the cartilaginous rings of the trachea and are extending into the surrounding portions of the lung. In other places the cells are more cuboidal and the nuclei are less spindle shaped. With the Bielschowsky stain, the connective tissue fibrils are distributed in the manner seen in carcinomata, and this is undoubtedly a carcinoma arising in a bronchus. The mass in the cerebellum proved to be a large metastasis. Other metastases were found in the lymph glands.

These three cases are obviously carcinomata arising from bronchial epithelium. In the first example, there is considerable mucin production, with an adenomatous arrangement of the cells in many places; in the second instance, the tumor more closely

¹ This case was presented as one for diagnosis, but further study revealed clearly its origin.

resembles squamous epithelium, and there is beginning keratinization. In the third case, the tumor histologically does not resemble the other two, yet its origin is quite definite.

2. Tumors Arising from Alveolar Epithelium

Case 4.¹ The patient, aged eighty-two years, was admitted to the City Hospital, Baltimore, Maryland, and owing to his inability to speak English, a history was never obtained. An examination showed impairment over the left lung posteriorly, with very distant breath sounds. He became progressively emaciated; there was accumulation of fluid in his left pleural cavity.

The left lung (autopsy No. 1453) was bound by recent adhesions to the pleura, and in these adhesions there was some hemorrhage. The lower lobe was compressed. The upper lobe was considerably increased in size; it was found to be filled with grayish-yellow tissue in which there were numerous necrotic areas. The outlines of the interlobular septa could be easily seen as pigmented bands passing back and forth. The alveoli were apparently filled with the new growth, producing a condition resembling pneumonic consolidation except in the color of the material filling them. The tumor extended up into the bronchus and completely filled the primary bronchus just where it divided into its main branches to the upper and lower lobes. The margin of the mass in the lung was slightly lobulated. Beneath the pericardium were numerous tumor nodules in the pleura.

This tumor is composed of medium-sized cells, having a relatively small amount of cytoplasm about the vesicular, oval nucleus. The cells are closely packed together. Mitoses are not numerous. The tumor completely fills the alveoli, but the alveolar septa can be readily distinguished, and strands of tumor are passing through the pores of Cohn. Where the tumor cells are closely approximated against the alveolar wall, they have a columnar arrangement. The tumor is extending through the lymphatics along the bronchi; it is also invading the mucosa. There is no keratinization; no demonstrable intercellular bridges and no mucin production in this tumor. Metastases are found in the parietal pleura, hylic lymph glands, mediastinum, and liver.

The mode of growth of this tumor, and the production of a condition resembling a carcinomatous consolidation of the lung, with the type of cells seen, point to the alveolar epithelium as the origin of this carcinoma.

3. Tumors Arising in Tuberculous Lungs

There are two examples of this condition.

Case 5.¹ A white woman, aged seventy-six years, was admitted to the Tuberculosis Pavilion, City Hospital, Baltimore, Md., with the complaint of

¹ I am indebted to Dr. T. R. Boggs and Dr. W. G. MacCallum of Baltimore, Md., for the privilege of reporting this case.

pain in the neck, and headaches. No definite history could be obtained because her statements were incoherent and conflicting. She was markedly cachectic, and there was advanced arteriosclerosis. The left half of the chest was immobile. There were signs suggestive of cavity formation in the left upper lobe. The sputum had a rusty tinge.

At autopsy (No. 1569), the left lung was densely adherent to the pleura by old fibrous adhesions. In the apex of the upper lobe there were several cavities with smooth gray walls. The lower part of this lobe was filled with a rather friable, gray tissue in which were collections of gelatinous-like material. In the terminal portion of the main bronchus, there projected a roughened tumor mass which practically completely filled it. The branch of the pulmonary artery passing over the bronchus was almost completely occluded by a hyaline thrombus, and the pulmonary vein was entirely filled with a mass of friable tumor which extended to hang as a tasselled plug in the left auricle.

In sections of the left lung, there are found many hyalinized tubercles encircled by considerable scar tissue containing much pigment. Surrounding and invading extensively these old tubercles is tumor composed of rather tall cells with oval, vesicular nuclei. These cells often are growing in rather dense masses, but even in these masses there is frequently found small or large collections of mucin. In other places, multinucleated cells are rather numerous and the tumor has a somewhat papillomatous appearance, where enclosing very large spaces. Mucin is present in these larger lumina. Mitoses are moderately numerous. There is extensive necrosis in many parts of the tumor. The tumor is extending up into the primary bronchus; it is replacing the bronchial mucosa. Metastases were found in the right lung, right kidney, and right adrenal.

Case 6. The second instance of carcinoma associated with an old tuberculous lesion occurred in a man, aged forty-two, who was admitted complaining of pain in the sacral region. He stated that this pain came on a short while after an injury.

His lungs were negative on physical examination. Neurological examination revealed weakness of the lower extremities. X-ray showed destruction of the intervertebral disc between the twelfth dorsal and first lumbar vertebræ, with destruction of the body of the latter vertebra. There was considerable mottling of the ribs, with mottling throughout the lungs, resembling calcium deposits due to old tuberculous lesions. Repeated examinations with the x-ray showed the lesions in the vertebræ to be progressing. While turning over in bed one day, he had a sudden sharp pain in the left clavicle, and a swelling appeared at this point. At a later date, while again turning in bed, he had a sudden pain in the back, and immediately thereafter complained of loss of sensation in both legs and thighs, with a band of hyperesthesia in the region of the tenth thoracic zone. This was followed by flaccid paralysis of the lower extremities and total loss of sphincter control of the bladder and rectum. His emaciation was quite rapid, and the pain was severe.

The autopsy (No. 9262) revealed the apex of the left lung bound to the parietal pleura by dense adhesions. At the apex of the upper lobe there was a calcified nodule, and anterior to it a moderately firm mass, 2.5 cm. in diameter, composed of rather gray tissue in which were found several small calcified

nodules. A moderate-sized bronchus entered into this mass. The lymph glands at the hilum of the lung contained tumor in which there was considerable gelatinous material. The right ilium was almost destroyed by tumor. There was involvement of the left clavicle where fractured. In the ninth rib on the left there was a large metastasis, and in the first, fifth, sixth, seventh, ninth, tenth, eleventh, and twelfth dorsal vertebrae and in the first, second, third, and fifth lumbar vertebrae there were numerous tumor nodules. The seventh and eleventh dorsal, the first and fifth lumbar vertebrae were almost completely destroyed. The sacrum too was extensively involved. At the level of the sixth dorsal vertebra, the spinal cord was very much softened and discolored, and in the cauda equina a tumor nodule, 2 cm. in greatest diameter, was found. Other metastases were found in the mesentery, omentum, peritoneum, bronchial and pelvic lymph glands, liver, spleen, kidney, adrenal, and pleura.

In a section from the apex of the left upper lobe there are found hyaline tubercles invaded by a tumor composed in places of rather large columnar cells with vesicular nuclei. These are often arranged in a palisade manner around the alveoli; in other places they are growing in rather broad sheets, while in other parts there is an adenomatous arrangement with the production of a mucin-like material. The tumor is extending into the lymphatics along the submucosa of the bronchus entering the tumor. It is invading the wall of the pulmonary artery nearby. In all of the metastases there is extensive mucin production.

In these two cases, there is very definite evidence of carcinomata arising at the site of obsolete tuberculous lesions. The first of these cases shows extensive invasion of the pulmonary vein, which has been described in carcinomata of the lung; the second is identical histologically and in its mucin production with the first described tumor arising from the primary bronchus (Case 1).

4. Tumors Arising in Bronchiectatic Cavities

In this series there is but a single instance of carcinoma arising in a bronchiectatic cavity.

Case 7. This was a man, aged forty, a Jamaican, who complained of cough and expectoration for eight months, shortness of breath, and pain in the left breast for one month. He dated his illness to the previous winter when after exposure he developed a cough which lasted for a month. After this he felt well for two or three months, when he developed a persistent cough, accompanied by an expectoration which was most profuse in the morning. Three weeks ago he began to have pain in his left chest.

Physical examination revealed consolidation of the left upper lobe. X-ray showed a large dense shadow extending from the third to the tenth ribs on the left, with displacement of the trachea. The lower portion of the lung

was air-containing. There was gradual increasing involvement of the lung. Bronchoscopy revealed no evidence of new growth in the lung. An exploratory thoracotomy was done; fatal hemorrhage occurred.

At the autopsy (No. 9073) the left lung was bound to the pleura by very dense adhesions. The upper lobe was considerably increased in size. It felt very firm. The main bronchus to the upper lobe was markedly constricted at one point; beyond this it was dilated, ending in a large cavity which was almost completely filled by an irregular tumor mass attached to the wall by a short pedicle. In the dilated portion of the bronchus there was found a second plug of tumor. The wall of the cavity was quite rough, and on the lateral surface was very thin. In the lower part of this lobe there were numerous bronchiectatic cavities filled with pus. The lower lobe was compressed.

The tumor is composed of cells resembling epithelium which are somewhat variable in size. Their nuclei are vesicular; in many there is very distinct hyperchromatism, with occasionally a large nucleolus. The cells are arranged in cords or masses, containing very little stroma. They often enclose spaces in which there is well-preserved blood. Mitoses are numerous. There are no metastases.

5. *Tumor of the Pleura*

Case 8. A man, aged thirty-seven, complained of cough and pain in the left chest. He dated the onset of his illness to a time three weeks before when he caught cold, at which time he had a slight cough but did not stop work. One week later he had pain in the left side, the cough became worse, and he lost fourteen pounds in the three weeks.

The physical examination showed dullness over the left chest, with decrease in the voice and breath sounds, and the presence of a friction rub in the left axilla. X-ray revealed increased density in the left lung, with a projection of the density from the mediastinum toward the axillary line. He developed complete paralysis of the left vocal cord. A friction rub was heard over the heart. There was a gradual decline in his condition, and he died six months after entering the hospital.

At autopsy (No. 9139) the mediastinum was found to be filled with a large mass which extended downward over the pericardial sac and reached upward above the left clavicle. The mass was adherent to the sternum; it lifted up the mediastinal pleura on the right, and was directly continuous with a layer of dense white tissue which seemed to enclose the left lung entirely except for a small space on the posterior part of the lower lobe. The lung was bound to the chest wall by this new tissue which was exceedingly tough. On section the lung was encased in a layer of very firm gray tissue, measuring up to 1 cm. or more in width. This new tissue held the lung rigidly. It entirely encircled the main bronchus and aorta, apparently compressing the aorta in the transverse portion of the arch. The tumor infiltrated into the primary bronchus, completely filling it, and extended upward into the lower part of the trachea. It passed down into the fissure between the two lobes. There were numerous bronchiectatic cavities in both the upper and lower lobes. The pericardium had been penetrated and tumor bound the lateral surface of the left ventricle to the pericardium. Large masses of tumor lay along the pulmonary artery and

grew down upon the surface of the right ventricle. The left auricle too was caught in the new growth.

Histologically, this tumor is composed of very small cells, with scant cytoplasm, and round or oval vesicular nuclei. The cells lie in large masses and frequently have an alveolar arrangement. The stroma is scant. About these masses of cells there are dense bands of connective tissue containing considerable black pigment. The lymphatics are filled with the tumor. The tumor is extending into the lung; masses of cells are found lying in many of the alveoli. In the bronchial, mediastinal, cervical, gastric, and left axillary glands are found metastases. In the epicardial fat is extensive tumor growth, and the veins and lymphatics in this layer contain tumor as do also the lymphatics in the myocardium.

This tumor differs markedly in its histology from those tumors previously described. The cells are much smaller, the cytoplasm is scant, and there is no mucin production. The main portion of the growth involves the pleura and it seems most likely that this is an alveolar sarcoma or preferably a mesothelioma arising from the pleura. The other possible sources for the growth, such as the mediastinum, lymph glands, and thymus, would seem to be excluded by the histological picture of the tumor.

Discussion:

DR. WOOD: It is difficult to make a histological diagnosis from lantern slides alone, but I wonder whether there might not be still another possibility in the tumor, Case 3, and that is that some thymic remnant may be responsible for the spindle-celled portion, and the other portion be a true carcinoma of the lung. I think we do not realize how often we find multiple tumors in tissues. They have been very much overlooked, and the regular occurrence of multiple tumors in animals hints that we will on further study find more multiple tumors in human beings. The production of multiple sarcomata in the liver by a single irritant in that liver is an interesting bit of experimental production of tumors, and independent sarcomata of two different types are occasionally seen in the walls of small cysticercus cysts in the liver of the experimental animals at the Crocker Laboratory, showing that synchronous tumors arise following irritation. I think this has been an interesting survey of practically all the types of tumors of the lung. There is still another type, and I wish I had thought to bring up sections and slides of this other form of tumor, which has not yet come to autopsy. The surgeon removed a considerable portion, and if it was put under the microscope without any definite statement that it came from the lung, I think that anyone would say that it came from a pigmented mole. It has exactly the same morphology, and yet the patient has no evidence of a pigmented mole which might give rise to the tumor. The morphology is different from anything shown here. I presume we will have to call it an atypical carcinoma arising from the bronchi, but in lieu of something better it has to be left as incompletely diagnosed.

DR. SEECOF: I would like to ask Dr. Von Glahn whether the chest fluid which was removed from one of the cases was examined for tumor cells. At the Montefiore Hospital we have a series of thirty-five lung tumors in 750

autopsies, and a frequent procedure there is when there is effusion in the chest to withdraw the fluid, and it is remarkable how frequently we find tumor cells in the fluid.

The other case that interested me was the pleural tumor. The question was raised in Boston whether any of these tumors are endotheliomata of the pleura.

DR. MACNEAL: I would like to ask Dr. Wood if the eyes were negative in the case he mentioned.

DR. WOOD: Yes.

DR. VON GLAHN: In regard to the question of a possible thymic origin in Case 3, I searched very carefully for thymus, and could not find any grossly. The mediastinum seemed to be clear, and the tumor did not penetrate beyond the capsules of the glands.

In regard to the case where the rib was resected for drainage of the pleural cavity, the fluid was frankly purulent. There was no search for tumor cells.

Whether there is such a tumor as a primary endothelioma of the pleura I can not state definitely. There are tumors which are classified by some as carcinoma arising from the pleura and which others prefer to call sarcoma or mesothelioma. In this case I thought that mesothelioma was the better term, because it seemed to be so definitely arising from the pleura.

SOME CHANGES OCCURRING IN ACCIDENTALLY TRANSPLANTED BONE

A. P. STOUT *

The behavior and fate of transplanted bone has been the object of investigation and the subject of heated discussion for many years. Although something is known concerning the morphological changes which may occur in a transplant under varying conditions, one finds in the literature very few attempts to explain these changes in terms of physical chemistry. With the hope of stimulating interest in this aspect of the problem of bone transplantation I propose to present to you a case in which bone has been displaced from its anatomical situation and violently transplanted into the soft parts, and to discuss the interpretation of the morphological picture in the light of physico-chemical hypotheses regarding calcification and ossification.

* From the Surgical Pathological Laboratory of the Presbyterian Hospital
Drawings by Alfred Feinberg.

A seventeen-year-old girl was swinging on the flying rings when she missed her hold and fell to the floor, striking on her left elbow. An x-ray picture taken a few days later showed that the head of the radius, including three fourths of the articular surface, had come to lie just below the external epicondyle of the humerus in such a way that the articular surface of the broken fragment pointed downwards and inwards. Eight and a half weeks after the fracture, the piece of bone was removed by operation. Dr. F. B. St. John, who did the operation, tells me that the fragment lay entirely outside the region of the joint, with the line of fracture fixed by vascular tissue to the subcutaneous tissue. We seem to have good evidence that this piece of bone and cartilage was forcibly torn from its attachments and driven into the subcutaneous tissue, where it subsequently became reattached along the broken end of the fragment.

When examined after removal, the fragment, covered on one end with its articular cartilage, corresponded to three fourths of the radial head and grossly

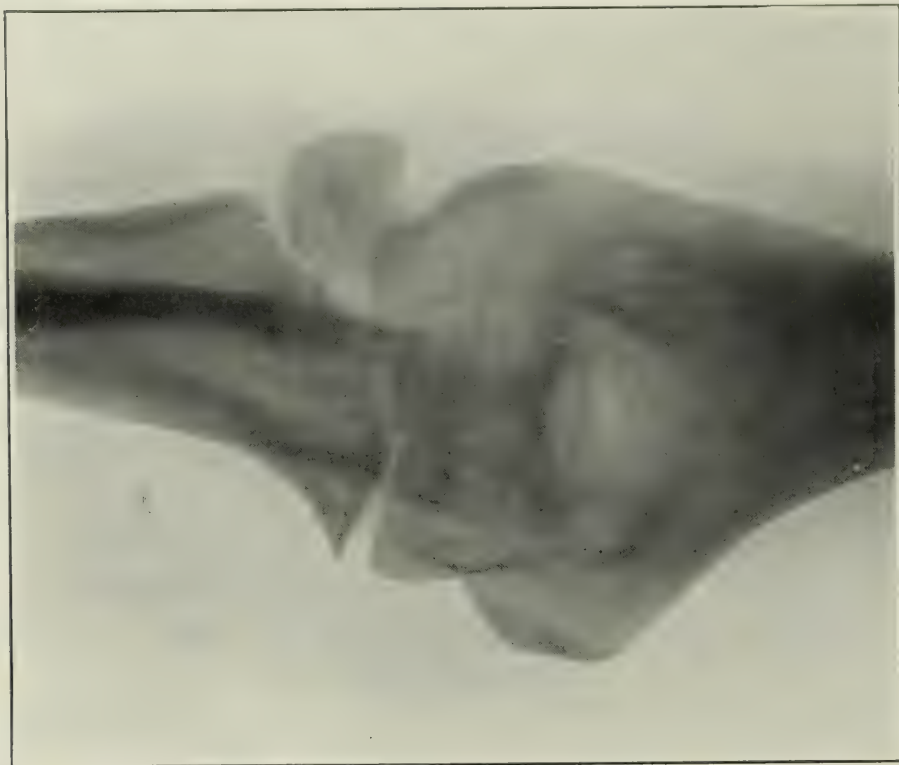


FIG. 1. D. W. Pres. Hosp. Hist. No. 54360. Antero-posterior radiograph of elbow joint showing fragment consisting of three fourths of radial head rotated through 180° , so that the articular surface points downward.

the only evidence of change was in the appearance of cartilage on the neck of the bone contiguous to the articular cartilage. Some fibrous tissue was adherent to it over the fractured surface which was quite jagged and irregular.

The microscopic picture is one of considerable interest. The section has been made in a plane passing through the long axis of the fragment. It will be seen that the general arrangement of bone and cartilage seems unaltered—a loose textured, spongy bone covered with hyaline cartilage. A closer examination shows that the trabeculae are composed of two parts—a central portion which stains a fainter pink, and in which the cell lacunae are empty, and an external deeper pink-stained layer which is laminated and in which there

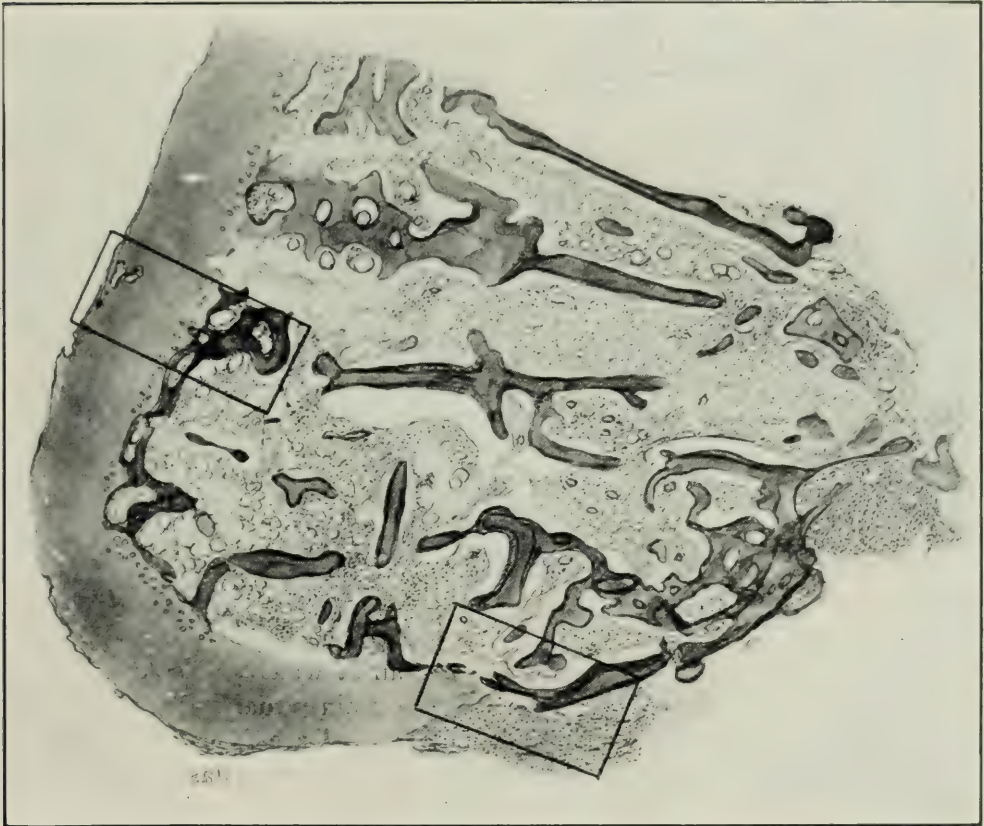


FIG. 2. Drawing of microscopic section made through the full thickness of the fragment. The articular cartilage is shown with its few staining nuclei near the junction of cartilage with bone. In the marrow spaces, fat cells and blood vessels can be distinguished. Most of the bone trabeculae show a central lighter zone surrounded by a darker margin.

are a good many lacunae, all of which are filled with bone cells. There are rows of so-called "osteoblasts," outlining some of these trabeculae, while fibroblasts seem to be in process of incorporation in others. A few osteoclasts are found in relation to the free spicules of bone along the line of fracture. Nowhere else can any be found. In the marrow spaces can be recognized with certainty fibroblasts, many thin-walled capillaries and fat cells. In addition there are many cells which have morphological resemblance to specific marrow

cells such as myelocytes and myeloblasts, although as no differential stain was made one can not record this as an accurate observation.



FIG. 3. Detail drawing from area indicated in the lower part of Fig. 2, where the articular cartilage joins the shaft of the bone. *A* = articular cartilage with nuclei staining. *B* = apparently new fibro-cartilage which has proliferated after transplantation. *CCC* = central portions of bone trabeculae which stain a faint pink and have few lacunae, all of which are empty. *DDD* = peripheral portions of bone trabeculae, which stain a dark pink, have many lacunae, all of which contain staining bone cells and are frequently outlined at their junction with marrow by a layer of so-called "osteoblasts." The spaces between bone and marrow are probably artefacts due to sectioning.

The cartilage covering the end of the bone appears as a homogeneous pink matrix with scarcely any nuclei or even nuclear spaces. There are a few spaces which seem to contain fibroblasts and possibly capillaries, and in the depths near the junction with bone, a few old cartilage cells remain. At the margin of the cartilage where it joins the bone and capsule, a distinct proliferation of cartilage has occurred, resulting in the formation of a new fibrocartilage which is covered with a perichondrium composed of compacted elongated cells. This new cartilage has descended over the head of the bone for an appreciable distance.

Before attempting to discuss the biological process which is represented by this morphological picture, it will be necessary, first, to recapitulate the probable antecedent morphological

changes through which the transplant may have passed, and second, to epitomize the recent hypotheses regarding the processes of calcification and ossification.

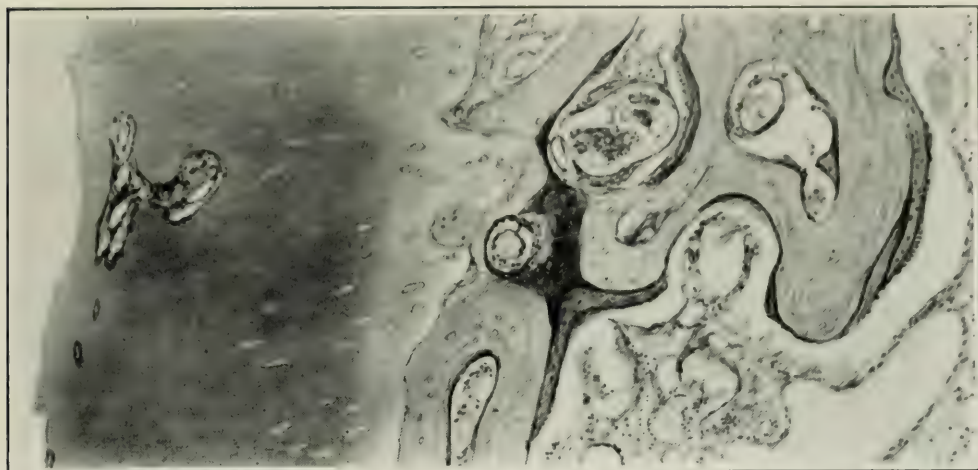


FIG. 4. Detail drawing from area indicated at the left of Fig. 2. At the left of this picture is the articular cartilage which takes a reddish stain, and shows lacunæ devoid of staining cartilage cells, except for a few near the junction with bone. Near the free surface is seen a space in the cartilage filled with connective tissue containing blood capillaries. The bone trabeculae show the same changes as in Fig. 3.

Recapitulation of Probable Antecedent Morphological Changes Occurring in the Bone Transplant

The following account has been based upon the many studies which have been made of surgically transplanted bone, both human and animal, by Phemister,¹ Bancroft,² Gallie and Robertson,³ Brooks,⁴ Matsuoka⁵ and Haas⁶ among others during the past ten years.

It may be assumed, therefore, that immediately following the injury, the fragment of bone lay in the subcutaneous tissues, either completely separated from its former attachments, or with some shreds of capsule still attached, but in any event, with its blood supply so seriously compromised as to be valueless. It was probably separated from the surrounding tissues by a layer of coagulated blood. Within a few days a large proportion of the bone cells and the characteristic marrow cells had disappeared, probably leaving only some of the connective tissue and endothe-

lial cells of the capillaries of the Haversian canals and marrow spaces and possibly a few bone cells in their lacunæ. Proliferation of these cells, together with proliferation of fibroblasts and capillaries from the surrounding connective tissues, soon reestablished a blood circulation within the soft tissues of the bone fragment. We may feel sure that the marrow was soon regenerated following transplantation, because of the work of Matsuoka⁵ who transplanted femur marrow into the spleen of the same animal successfully in thirty successive rabbits; while Bunting,⁷ Nicholson⁸ and Asami and Dock⁹ have proved the presence of true red marrow in heteroplastic bone formation.

Almost from the moment of transplantation, probably, there began that interesting process of the simultaneous resorption of old bone and deposition of new lamellated bone in its place, to which Marchand has given the descriptive term of "creeping replacement." It is supposed that there occurs a deposition of new bone about connective tissue cells which are adjacent to the old bone trabeculæ and at the same time the old bone disappears progressively from its periphery towards its center.

Had there been some new bone proliferation about the fracture end of the fragment it would not have been cause for surprise, inasmuch as it has been frequently shown that extrasketal transplants of bone, or marrow, may for a time initiate the formation of new bone in relation to them (Matsuoka,⁵ Barth,¹⁰ etc.).

We cannot venture to predict the fate of this extrasketal bone transplant, had it been allowed to remain in the tissues, with any degree of certainty. Bone transplanted extrasketally and lacking the so-called "functional stimulus" tends to atrophy and disappear. It may do so very slowly, however, as Ely¹¹ found a bone fragment transplanted into the thigh muscles persisting after 1,103 days and it is quite conceivable (in the light of heteroplastic bone formation) that under some circumstances it might persist indefinitely.

*Recent Hypotheses Regarding the Processes of Calcification
and Ossification*

It will be necessary next to summarize very briefly the recent hypotheses regarding the ordinary processes of calcification and ossification. Of necessity the discussion must be confined to the processes actually occurring at the site of ossification in a relatively normal individual.

It has been stated by Wells,¹² Freudenberg,¹³ György¹⁴ and others that before ossification or calcification can occur there must be first a hyaline matrix. The other essential is the existence in the blood, and presumably in the tissue fluids, along with a few other inorganic ions, of a solution of calcium ions and bi-phosphate ions in such a state that their solubility product is just below the precipitation point of tricalcium phosphate. These ions are held in solution in the serum because of its degree of hydrogen ion concentration.

It is supposed that this serum containing the calcium enters the hyaline matrix where, because of colloidal combination, it comes to exist in greater concentration than in the blood. But in the hyaline matrix the number of cells per cubic volume is relatively small, hence the metabolic rate in this area is assumed to be unusually low, resulting in a lowering in the carbon dioxide output. It is supposed that with this there occurs a decrease in the hydrogen ion concentration, whereupon an insoluble tricalcium phosphate is precipitated in the matrix together with calcium carbonate and the other inorganic salts.

Conversely, it has been assumed that demineralization occurs by a reversal of this process; that is, an increase in the hydrogen ion concentration (*i.e.*, increased acidity) causes the tricalcium phosphate to go into solution once more. Nicholson,⁸ so far as I know, is the only one who has offered any hypothesis to explain how hydrogen ion concentration may be locally increased. He suggests that osteoclasts, because of their many nuclei, have a high metabolic rate; consequently the acidity in their immediate vicinity may be increased resulting in a demineralization of bone. This hypothesis will not be acceptable to those who, like Arey,¹⁵

believe that osteoclasts are not active cells at all but are simply syncytial masses of fused osteoblasts undergoing degeneration. In any event this hypothesis can not be used to explain the decalcification which may occur without discoverable osteoclasts.

Discussion of the Changes Observed in the Transplant

If it is assumed that "creeping replacement" in a transplant occurs as has been stated by a removal of calcium from the trabeculae to new formed bone about them, the problem necessitates the explanation of at least two steps. First, there must occur a change in the physical state of the calcium, phosphate and other inorganic ions so that they become soluble and diffusible. Second, there must occur a reversal of this process along the margin of the trabeculae so that the ions will be reprecipitated in this new situation. From the work which has been done upon the processes of calcification and decalcification one must suppose that the controlling factor in both is the degree of hydrogen ion concentration; in the first instance it must be increased and in the second it must be decreased.

In casting about for an explanation of the increase in hydrogen ion concentration, it is possible to suppose that the source of this may be found in the metabolism of cells. At the moment of transplantation of this fragment the shock of the trauma probably reduced the metabolic rate of the cells to a very great degree. With the subsequent proliferation of the cells in the intertrabecular soft parts, the metabolic rate was probably greatly increased and hence the hydrogen ion concentration of the area was correspondingly increased. It may be supposed that this was quickly regulated throughout most of the soft tissue of the fragment by the reestablishment of a blood circulation but at the very line of junction with the bone, where there was observed a line of closely placed cells, it is possible that there may have been sufficient increase in local hydrogen ion concentration to affect the most adjacent precipitated tri-calcium phosphate of the old bone trabeculae.

In order to explain the decrease in the hydrogen ion concentration along this same line of active cells, one has to suppose not

only that their metabolic rate is greatly decreased, so that the surrounding acidity is reduced, but also that a new hyaline matrix is formed about the connective tissue cells most adjacent to the old bone. With this decrease in acidity the calcium and phosphate ions will be reprecipitated as a new-formed insoluble calcium phosphate in the new hyaline matrix.

I can find no adequate explanation of the process which causes the change in intercellular substance leading to the formation of a hyaline matrix. All of the observations upon growing bone, reparative bone and heteroplastic bone, however, tend to confirm the statement which has often been made that the formation of a hyaline matrix precedes ossification.

That a blood circulation is an essential feature of this process may be assumed if a comparison is made between what has apparently occurred in this transplant and what seems to occur in heteroplastic bone formation in relation to areas of calcification in the body. As has been shown by Moschcowitz,¹⁶ Nicholson⁸ and many others, bone does not seem to form in relation to an area of pathological calcification unless it is first invaded by vascular granulation tissue.

In conclusion it is necessary to emphasize that no formula or hypothesis of reactions can be complete unless it takes into account all of the immediate and remote factors which are constantly operating to modify it. Inasmuch as only a few of these factors are known or suspected in this case, any such attempt as the above to explain the process of "creeping replacement" in a transplant must remain a pure speculation.

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THE EFFECT OF RADIOTHERAPY IN A CASE OF HODGKIN'S DISEASE

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This is a case of interest for the following reasons:

1. The spleen is believed to be unusually large for this disease.
2. The blood count is similar to that described by Bunting.
3. The apparent effect of radiotherapy on the clinical course and histology of the glands is noteworthy.

The patient, E. H. (history 47810; autopsy 9202), was an American school-boy of thirteen, who was admitted on September 30, 1920, complaining of enlarged glands.

The family history was irrelevant.

There was a history of double otitis media four years ago, and of the usual diseases of childhood.

About three and a half years ago glands began to enlarge slowly. Two and a half years ago glands were removed. Later others began to increase in size, and in a year were as large as those taken out. The first glands involved were those of the neck; at the time of admission the axillary glands were enlarged. The glands were painless. He had fever at intervals.

Physical examination in the Out-Patient Department on September 21, 1920, showed a rather under-developed boy. The heart was enlarged; there was a soft systolic murmur at the apex, not transmitted. The lymph glands in the left side of the neck and those in the axillæ were enlarged and adherent. The masses were soft, not fluctuating. The spleen was hard, easily felt, and was about 3 cm. below the costal margin. X-ray of the abdomen was negative for calcified glands.

On October 25, 1920, under general anesthesia, an axillary gland was removed for diagnosis. The patient was given x-ray therapy at frequent intervals.

Microscopic Examination: The section through the lymph gland showed that the normal architecture was completely changed. There were no lymph follicles to be made out, and the germinal centers had disappeared. There was an increase in the amount of connective tissue, and the lymphoid cells were scattered throughout. There were areas where numerous eosinophiles could be seen, and with the high power, typical cells as described by Reed were found. There were no areas of coagulation necrosis. The diagnosis of Hodgkin's disease was made.

The x-ray reports showed no sign of calcified glands in the neck. The upper mediastinum showed a slight increase in density. The trachea was not displaced. The linear markings in the right upper lobe were accentuated.

The blood Wassermann was negative with both antigens.

The urine examination was negative.

Radiotherapy (under the direction of Dr. Witherbee): The body was divided into twelve areas, six anterior and six posterior. In addition, the neck was exposed on both sides. By treating half of the trunk in front and back at one sitting the whole of the body was treated during two exposures. The neck and axilla were treated as often as it was thought necessary without danger of burns. The formula was spark gap, six inches; current, 80 kilo volts; anode skin distance, 10 inches; tube, Coolidge; exciting apparatus, Solace; filter, 3 mm. aluminum. The exposures lasted two minutes, occasionally two and a half minutes.

Blood Counts

	9/30/20	11/1/20	11/11/20	1/11/21	3/22/21	4/26/21
Red cells.....	5,600,000	—	—	—	—	—
Hemoglobin.....	75%	—	—	—	—	—
White cells.....	9,000	13,000	11,000	4,200	5,000	4,600
Platelets.....	—	—	400,000	405,000	285,000	275,000
Neutrophiles.....	78	68	47.8	63.4	68.8	44.7
Eosinophiles.....	1	0	7.8	3	7	10
Basophiles.....	0	0	0.4	0.6	1.2	0.6
Lymphocytes.....	18	32	34.8	22	15.2	37.7
Transitionals and large mononuclears	3	0	7	7.6	7.2	7
Unclassified.....	0	0	1.8	3.4	0.2	0
Myelocytes, neutro- philes.....	0	0	0.4	0	0.4	0

For a while he seemed to improve. In January, 1922, he began to fail rapidly and was confined to his bed. He had severe abdominal pain, accompanied by nausea and vomiting. The heart was enlarged. The spleen was enlarged and tender. The legs were swollen. He grew worse and died January 28, 1922.

Autopsy 9202. The heart does not appear to be increased in weight. The right side is considerably dilated. There is no excess of fluid in the pericardial

sac. The epicardium is everywhere smooth and glistening. The valves throughout are thin and delicate. The myocardium is extremely pale in color. There is marked tigering of the inner surface of both ventricles and on section considerable fat is seen in the muscle. The blood is very pale and watery, and there are only small post-mortem clots found.

The spleen is greatly enlarged. It is non-adherent. The capsule is smooth and does not wrinkle. The surface is lifted up in places by slightly grayish nodules. On section the pulp is found to be studded with irregular masses, some of which are grayish-red; others are white. These masses are quite irregular in outline and project above the cut surface. The Malpighian bodies are not seen. The pulp between these masses is dark red in color. The spleen weighs 650 gm.

The liver is slightly enlarged. There is a deep scar, somewhat radiating in character, on the anterior surface of the right lobe. Below this scar, there extend into the liver for some distance bands of connective tissue. The liver substance is quite pale. There is an apparent increase in fat throughout the organ.

The kidneys are rather large. The capsule strips readily. The cortex is very pale. The striations are regular but not very distinct. The striations of the pyramids are more distinct than those in the cortex. The glomeruli are not readily seen. The pelvis is negative.

The glands in the neck, axillæ, and groin are greatly enlarged. The glands in the axillæ are discrete; they are easily separated one from the other. They are moderately firm, though not cutting with increased resistance. The cut surface is rather homogeneous, yellowish-white. There is no necrosis made out, nor is there any increase in connective tissue. In the upper anterior mediastinum, there are large masses of glands which are discrete and together form a mass extending from the supra-sternal notch to the heart. This mass measures 10 cm. in length by about 6 cm. in width. On section they resemble the axillary glands. The retroperitoneal glands along the aorta are greatly enlarged, and on section appear as the glands elsewhere.

Microscopic Examination of the spleen shows the Malpighian bodies are not very distinct. They appear to have been entirely replaced by connective tissue which is very dense and in which are often found large phagocytes loaded with a bright brown granular pigment. Giant cells with large solid nuclei are found in these areas (Figs. 1 and 2). In a few instances where the Malpighian bodies are made out, they contain an unusual number of polymorphonuclear neutrophiles and eosinophiles, and in these areas are large cells with oval or indented vesicular nuclei and prominent nucleoli. In places in the pulp there are foci where the connective tissue is increased, and in these areas is seen an occasional typical endothelioid cell, as described above. There are also areas in the pulp in which only the shadowy outlines of cells remain, and in these areas of necrosis, there are pyknotic nuclei, fragments of nuclei, and hemorrhage. In other places there are areas somewhat resembling these, but in which there is hemorrhage, with phagocytes containing pigment nearby. Occasional clumps of typical endothelioid cells are seen. These are, however, relatively infrequent. The striking thing about the pulp is the great number

of neutrophilic and eosinophilic leucocytes. These in places are collected together into moderately dense masses. The blood vessels in the spleen, both the larger and smaller vessels, are packed with leucocytes of the same varieties.

There is an irregular distribution of fat throughout the section of the liver. In some places the fat-containing cells are about the efferent veins; in other places, about portal spaces. The cells about the efferent veins are generally rather pale; the cytoplasm is granular and stains faintly, and many



FIG. 1

of them contain large vacuoles. The cells about portal areas are much better preserved. There are small foci, apparently portal spaces, densely infiltrated with eosinophiles, and with an increase in connective tissue. In some of these areas there are found large cells with very dense hyperchromatic nuclei, but in none are there any typical endothelioid cells.

In another section through the scar on the anterior surface, there is a deep depression in the surface beneath which the parenchyma has disappeared and

been replaced by a moderately dense connective tissue. Numerous bile ducts are present. About many of the portions which were evidently portal areas, there are enormous accumulations of eosinophiles, such as were seen in the previous section. In these areas occasional large cells are found, which are not typical Reed cells. In the remainder of the section there is considerable fat in the liver cells. The portal spaces are infiltrated with eosinophiles and a few polymorphonuclear neutrophils. The connective tissue is increased within the spaces, and an occasional fairly typical endothelioid cell is found. The sinusoids in many places are quite filled with polymorphonuclear leucocytes.

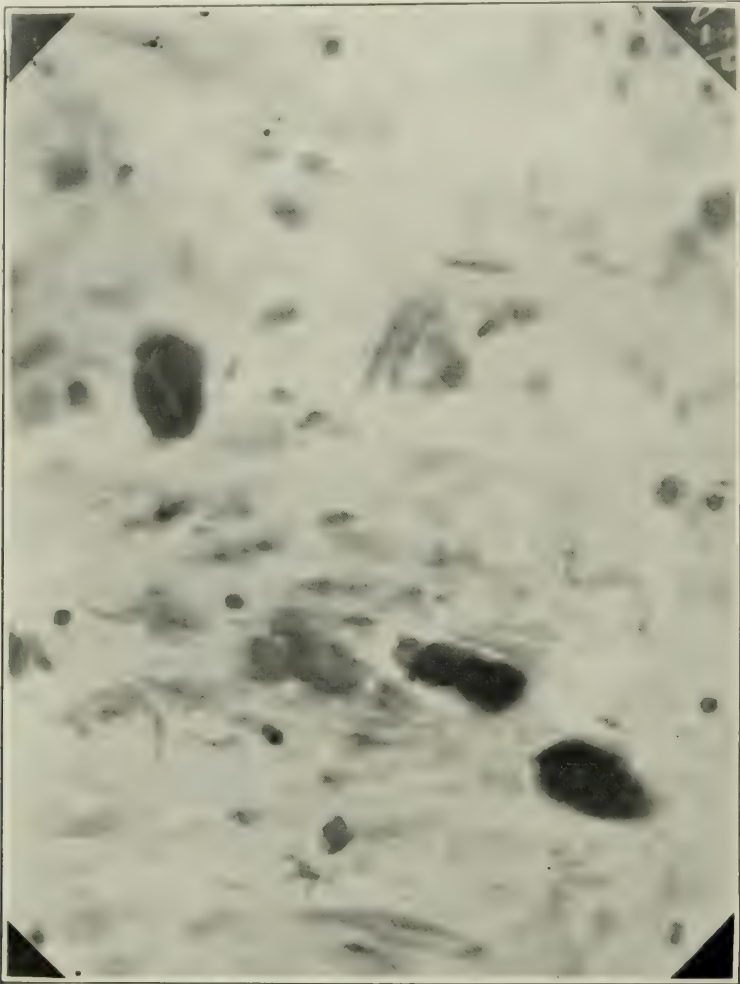


FIG. 2

The architecture of the glands has been entirely changed. There are not found any germinal centres, the sinuses are not to be distinguished, and there is very little lymphoid tissue left. There is a diffuse and widespread connective tissue increase, and scattered throughout the gland are found many large cells with one or more vesicular nuclei, each nucleus containing a single large nucleolus. A few of these giant cells have somewhat hyperchromatic nuclei.

There are only a few lymphoid cells seen. There is, however, everywhere a marked infiltration with eosinophilic leucocytes. The infiltration with leucocytes is a very prominent feature of the section. The vessels show slight thickening of their walls. The capsule of the gland is also thickened. There is no invasion of the capsule, and no extension of the process to the surrounding fat.

In another section, other changes are seen. There are areas of necrosis, with considerable nuclear fragmentation and pyknosis of nuclei. The Reed cells in this section are quite typical. There are practically none which show hyperchromatism. Eosinophilia is again a very marked feature.

In a third gland, the fibrosis is more marked than in the previous sections. There are no areas of necrosis. A few of the endothelioid cells show hyperchromatism of the nuclei.

In other sections the changes are the same as in the first described gland but the endothelioid cells are more abundant, some showing hyperchromatic nuclei.

Final Diagnosis: Hodgkin's disease.

In many respects this case may be said to present a classical picture of Hodgkin's disease, and in spite of this there was a loss of valuable time before it was correctly diagnosed. It was over three years from the time the boy was first seen until the diagnosis of Hodgkin's disease was made.

Early differential diagnosis between Hodgkin's disease and tuberculous glands of the neck is not always easy, ^{2, 3, 4, 5, 6} to mention only a few of the more recent contributors. The final diagnosis is generally admitted to be definite only when sections of the gland are available for histological examination. Cunningham ⁴ advises that more than one gland be examined whenever practicable. The histology has been discussed at length by MacCallum, ⁸ Longcope, ⁹ Reed, ¹⁰ Sternberg, ¹¹ and Ewing. ¹²

Bunting ¹ has done some very careful work on the examination of the blood and believes that a diagnosis can be made from a white cell count and examination of a smear. This may be true in the case of so skilled an observer, but as a rule the consensus of opinion seems to be that the blood count is suggestive rather than diagnostic (Longcope and McAlpin, ² and Pepper ³).

The increase in platelets, transitionals and eosinophiles is very well illustrated here. Unfortunately, the eosinophilia is discounted by the presence of an intestinal parasite. Even though one does not agree with Bunting it certainly would seem that the blood count in Hodgkin's disease is worthy of attention.

Physical Examination: There was nothing unusual about the size or distribution of the cervical lymph nodes. It is of interest to note that the enlarged mediastinal glands were not noticed on physical examination.

Heart: The marked increase in the signs of a heart lesion, observed a few days before death, was undoubtedly due to the fatty infiltration of the myocardium and a relaxation of the valve rings. Although there was a loud aortic murmur, as well as thrill, the valves showed no changes. Nothing resembling Hodgkin's disease was noted in the heart muscle.

Spleen: Large spleens are not unusual in Hodgkin's disease (Weber,¹³ Reed,¹⁰ Ewing,¹² Arning¹⁶), but it is thought that this spleen is proportionately very large. It weighed 650 grams and the boy weighed only about eighty pounds. On the other hand, primary enlargement of the spleen is rare in this condition. Authentic cases have been reported by Symmers¹⁵ and Mellon.¹⁴

Itching: This is not at all infrequent in Hodgkin's disease and sometimes as in this case (when the legs itched excessively), there is no demonstrable skin lesion.^{2, 17, 18, 19, 20, 21, 22, 23}

Temperature: Very probably judging from the mother's reports, the temperature was intermittent, and sometimes very high for a few days, resembling the so-called Pel-Epstein type.^{2, 24, 25, 26, 27}

Night sweats have been noted before. Ewing¹² calls attention to them.

Pain is difficult to explain, but it has been described before (Longcope and McAlpin²).

Course under treatment: The boy lived for fourteen months after the diagnosis of Hodgkin's disease was made (*i.e.*, about four years and eight months after first being seen). At first he seemed to improve and the glands decreased in size. He was usually very much upset by the radiation and frequently vomited soon after the treatment. He continued to improve for about seven months, then he commenced having attacks of pain in the back and thighs accompanied by high temperature. It is said that his skin showed some changes in color, but there were no satisfactory observations of this.

During the next two months he continued to lose ground slowly, but apparently the glands did not increase much in size. When last seen a few days before death he was very cachectic and evidently anemic. The glands had increased markedly. There appeared to be fluid in the abdomen, the ankles were edematous, and the cardiac condition seemed to be very much worse. Owing to the fact that this patient would not come to the hospital, the record is of necessity incomplete. This is to be regretted, first, because there is no record of the temperature which was undoubtedly intermittent, and second, a final blood count could not be obtained.

SUMMARY

1. The case is one of Hodgkin's disease diagnosed as tuberculosis of the cervical lymph nodes four and one half years before death.

2. He was treated for fourteen months by x-ray, apparently with benefit.

3. The spleen was tremendously enlarged and showed Hodgkin's disease tissue.

4. The endothelioid cells were apparently affected by the x-ray.

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PNEUMONIA IN NEWBORN INFANTS WITH LESIONS RESEMBLING INFLUENZA

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On account of the uncertainty as to the cause of epidemic influenza, and the almost constant presence, in the lungs of fatal cases, of streptococci, pneumococci, or influenza bacilli, it has been difficult to distinguish the lesions produced by the influenza virus from those which should be attributed to other organisms. Among the characteristics which have come to be regarded as rather typical of influenzal pneumonia, such as edema, hemorrhage, and necrosis of bronchial mucosa and alveolar walls, one lesion has attracted particular attention. This is the presence of a peculiar hyaline membrane, lining and adherent to the walls of dilated alveolar ducts and alveolar sacs. The membrane appears to be composed of an exudate, with which is fused necrotic material from the underlying wall of the air passage where it is attached. This hyaline membrane is not constantly present, nor is it uniformly distributed throughout the lung, but it is usually present in some parts of the lungs of patients dying during the early stages of the disease.

Goodpasture¹ in 1919 believed that the lesion is peculiar to the pulmonary inflammation of influenza, and that it does not occur in any other disease. Somewhat similar, if not identical, structures have been observed in the lungs of individuals dying after inhalation of war gases, and have also been produced experimentally in rabbits by intrabronchial insufflation of hydrochloric acid.² Professor Hayashi, of the Aichi Medical School, Nagoya, Japan, has informed me that he has seen the same thing in cases of plague pneumonia. In all these different conditions one etiological factor stands out prominently, that is, exposure to some agent which exerts a strong irritative and destructive action on the walls of the air passages.

Among the autopsies on the newborn at the Sloane Hospital during the past three years several cases have come to my attention in which the lungs presented lesions resembling influenza, especially in the presence of a similar hyaline membrane.

CASE I. (S-A-728.) *History:* The mother was in good condition at the time of delivery and had not had influenza. The Wassermann was negative. The duration of labor was seven hours. The membranes ruptured spontaneously and the child was delivered normally nineteen minutes later. Immediately after birth the child appeared to be in good condition, but about ten minutes later began to have rapid respiration and cyanosis. It was tubbed in hot water and improved temporarily, but had recurring attacks of cyanosis and dyspnoea, and died fourteen hours after birth.

Autopsy, May 20, 1920, by W. C. Johnson. The body was that of a premature infant weighing 2,250 gm. There was marked cyanosis, and all the organs were congested. The lungs together weighed 58 gm. They were dark red, firmer, and fleshier than normal. The right lung sank in water, the left barely floated. Crepitation could not be detected. There were several petechial hemorrhages in the pleura. On section a moderate amount of reddish fluid escaped from the cut surface, which was dark red. There were no patches of consolidation. The trachea and bronchi appeared congested, and contained a small amount of reddish frothy fluid. The larynx showed congestion and slight edema; not enough to produce any obstruction to respiration.

In microscopic sections the blood vessels throughout the lung were congested. The alveoli were poorly expanded. Most of them contained a granular material, a few red cells, and a very few polymorphonuclear leucocytes. The alveolar ducts were dilated, and were generally lined by a layer of red-staining hyaline material. (See Fig. 1.) This layer was also present in some of the alveoli. A similar layer was present in one small bronchus, overlying the epithelium. Two other bronchi contained plugs of red-staining material. A few groups of alveoli were filled with hemorrhage. The hyaline layer lining the

alveolar ducts appeared to be produced by a condensation of granular material. A few leucocytes were embedded in it. In many places fragments of hyaline material were seen lying free in the lumina of the alveolar ducts or alveoli. Necrosis of the walls of the air passages was not evident. In sections stained by Gram's method no bacteria could be found. There were no other lesions of any importance.

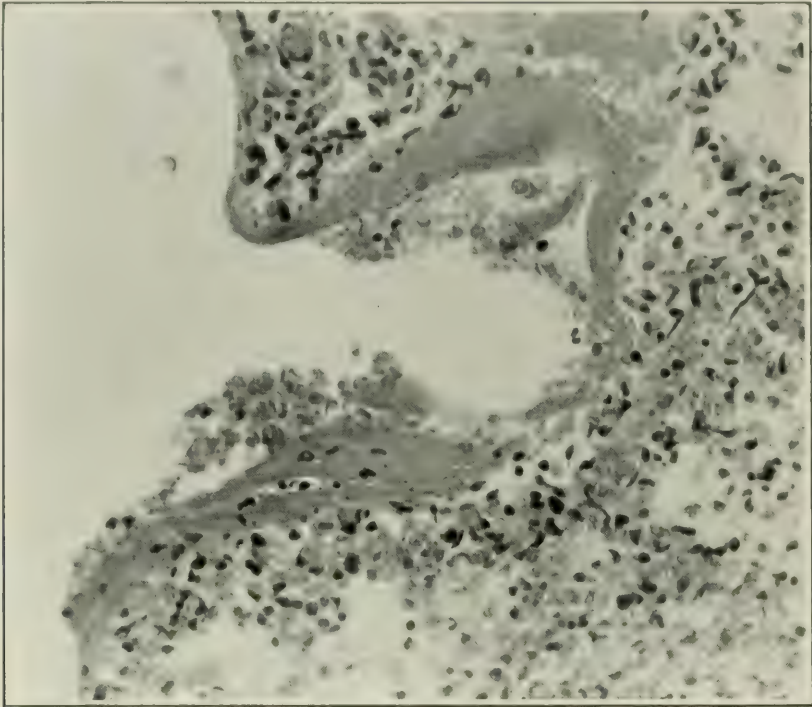


FIG. 1. Case I. Hyaline membrane lining dilated alveolar duct and alveolar sac in lung of infant dying fourteen hours after birth. High power photomicrograph.

CASE II. (S-A-812.) *History:* The mother was in practically normal condition and gave no history of influenza. The Wassermann was negative. After being in labor about fourteen hours she was delivered of twins by an easy breech extraction. The first twin appeared normal and survived. The second twin was in a state of "asphyxia pallida" at birth. One half hour later it became cyanosed, was placed in incubator, and did fairly well. Twenty-six hours after birth it became cyanosed again, and was given mustard bath but did not respond and died twenty-six and one half hours after birth.

Autopsy, March 10, 1921, by R. N. Pierson. The body was that of a premature infant weighing 2,250 grams. The only lesions of importance were in the lungs. They were firm, poorly aerated, but floated in water, and weighed 48 gm. The cut surfaces were red and bloody.

Microscopic sections of the lungs showed dilated alveolar ducts, many of which, as well as some of the alveoli, were lined by a hyaline membrane, which

in most places was not attached to the walls of the air passages. Many red corpuscles and some shreds of material suggesting remains of squamous epithelial cells were embedded in it. The majority of the alveolar ducts and alveoli contained a considerable amount of granular material, together with numerous red corpuscles, some of which were hemolyzed. Only an occasional polymorphonuclear leucocyte was present. There was no fibrin, and a Gram stain showed no bacteria.

CASE III. (S-A-817.) *History:* The mother was in good condition, with no history of influenza. The duration of labor was five and one half hours. The membranes ruptured only eleven minutes prior to delivery. The child never cried lustily. There was some bleeding from cord. The respirations were shallow, and color dusky and livid. It was given three mustard baths and died fourteen hours after birth.

Autopsy, March 24, 1921, by R. N. Pierson. The body was that of a premature infant weighing 2,480 grams. The lungs together weighed 51 gm. They were dark red and had a fleshy consistency. All lobes sank in water except the left upper, which showed marked interstitial emphysema. The cut surfaces were dark red and moist.

Microscopic sections of lungs showed dilated alveolar ducts, and some alveoli, lined by a layer of hyaline material. While a large proportion of the alveoli were not expanded the remainder contained granular precipitate and a moderate number of mononuclear cells, with a few polymorphonuclear leucocytes and red cells. The blood vessels were all congested.

CASE IV. (S-A-973.) *History:* The baby was one of twins delivered by Cæsarean section on account of flat pelvis. It had difficulty in breathing from the time of delivery, and died twenty-three hours after birth. The other twin survived.

Autopsy, May 6, 1922, by J. S. Wagner. The body was that of a premature infant weighing 2,125 gm. The lungs were heavy and poorly aerated, they weighed 63 gm. On microscopic section the alveolar ducts and sacs were markedly dilated, and many were lined by a narrow layer of red-staining homogeneous material. Many of the alveoli were not expanded. Some contained a small amount of granular precipitate, and an occasional squamous epithelial cell. No bacteria could be found.

It will be noted that the hyaline membrane described in these cases differed from that of influenza lungs in that it was associated with comparatively little necrosis of the underlying walls of the air passages. It appeared to be produced by a condensation of a granular precipitate, probably derived from an inflammatory edema, but possibly also from aspirated amniotic fluid. With this were fused a variable number of cellular elements, including red cells, respiratory epithelial cells, polymorphonuclear leucocytes, and aspirated epidermal epithelial cells from amniotic fluid.

While the lesions, on the whole, showed a striking resemblance to the bronchopneumonia of epidemic influenza, the existence of a true influenza infection seems improbable. In none of the cases could infection be traced to the mother, nor, so far as we could determine, were any cases of influenza present in the hospital at the time. Unfortunately no cultures were made from the lungs, and therefore ordinary bacterial infection cannot be excluded, but no organisms could be found in the sections.

A possible explanation which appeals to me more strongly is that the lesions were the result of the aspiration of some irritating substance, probably during labor, or birth. Analysis of the cases has failed to indicate definitely the nature of this injurious agent. In none of the sections did there appear to be any excessive aspiration of amniotic fluid, as shown by the presence of large numbers of epidermal cells. Moreover, in the lungs of the newborn in which such aspiration has occurred a reaction of this type has not been found.

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PERITONEAL REACTION TO CONTENTS OF RUPTURED HEMORRHAGIC CYST OF OVARY

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Until recently, collections of blood within cavities in the ovary have usually been regarded as hemorrhages into cystic and degenerating follicles or corpus luteum cysts, or as interstitial hematomata in the ovarian stroma. Two years ago, Sampson¹ directed attention to another important group of hemorrhagic ovarian cysts, the true nature of which had apparently never been fully recognized.

It had previously been noted that the effusions of blood into

these cavities sometimes occurred at the menstrual period, and that occasionally these blood cysts ruptured and discharged their contents into the peritoneal cavity. In the study of a series of perforating hemorrhagic cysts developing in women during the latter part of menstrual life, between the thirtieth year and the menopause, Sampson observed that most of them were lined, in part at least, by columnar epithelium, which in places showed glandular structures surrounded by stroma cells producing an appearance closely resembling endometrium. He interpreted the hemorrhage into the cysts as menstrual flow, the retention and accumulation of which produced gradual distension, and eventually rupture. Irritation of the peritoneum by the material escaping produced pelvic adhesions and sealing of the perforation in the cyst wall. At operation the cysts were usually again ruptured in freeing them from adhesions, with escape of a brownish fluid resembling chocolate syrup.

In addition to recognition of the endometrial nature of these cysts, Sampson^{1, 2} is also to be credited with the discovery of an association between the cysts, and adenomata or adenomyomata of the rectovaginal septum, intestinal wall, and peritoneal surface of the uterus. He believes that these cysts and adenomata are derived from fragments of epithelium of the endometrium or mucosa of the Fallopian tube, which through back flow of menstrual blood have escaped from the fimbriated extremity of the tube, and have become implanted in the ovary or peritoneum. The pelvic adenomyomata are usually derived from secondary implantations of epithelium cast off from the lining of ruptured ovarian cysts. In cases operated on during the menstrual period Sampson was able to find, in the lining of the ovarian cysts, histological changes corresponding to those in the endometrium of a menstruating uterus. In one patient, operated on during pregnancy, he found a typical decidual reaction of glands and stroma in three places—in the uterus, in the lining of an ovarian cyst, and in an adenoma on the posterior surface of the uterus.³

Sampson does not believe that many of these cysts of endometrial or Muellerian type are derived from congenital inclusions

of portions of the Wolffian or Muellerian ducts, or that they are due to invasion of cavities by extensions of the surface epithelium of the ovary, nor does he favor the "serosal theory" that pelvic adenomyomata are derived from a metaplasia of peritoneal mesothelium. He has largely rejected all of these views in favor of the single comprehensive implantation theory which I have quoted.

In spite of the rather sensational character of Sampson's theories, they have been very favorably received, and already a number of reports by Bell,⁴ Donald,⁵ Shaw and Addis,⁶ and Meigs,⁷ of other series of cases have confirmed his chief observations as to the endometrial nature of the so-called chocolate cysts, and their association with pelvic adenomyomata. Jacobson⁸ has furnished evidence supporting Sampson by experiments on rabbits, showing that implantations in the ovary and peritoneum of small pieces of tissue removed from the endometrium will develop into cysts.

In the examination of pathological material from the Sloane Hospital, during the past year and a half, we have watched with much interest for ovarian hematoma of this type, and in several cases have found very small unruptured blood cysts lined by columnar epithelium with an occasional gland surrounded by stroma cells. Very small unruptured cysts of this type are apparently quite common and may be overlooked, a fact which even Sampson himself did not recognize at the time of his first publication, as he has since admitted. The specimens reported here illustrate some of the features described by Sampson and others. While they do not shed any additional light on the question of epithelial implantation they are of particular interest because of the peculiar lesions produced by the reaction of the peritoneum to the contents of a large "chocolate cyst," which had evidently ruptured not long previous to the time of operation. I have not been able to find a description of just such a picture either in the recent papers on "chocolate cysts" or in the accessible literature of the older studies of pelvic hematocele. The patient was operated on at the Sloane Hospital by Dr. W. E. Studdiford, to whom I am indebted for the data on the case.

The patient, forty-one years of age, had complained of pain in the right side for four or five years, but menstrual periods were regular, every twenty-eight days, lasting four days, with no pain. She had intermenstrual pain which had been increasing for eighteen months, and also noticed loss of strength and feeling of pressure in the pelvis.

At the operation, both ovaries were found to contain large cysts, the left one in the cul-de-sac and the right one lying in the false pelvis. There had been a rupture of the right cyst with a discharge of chocolate-colored material, masses of which were adherent to the intestine, ovaries, and uterus. Adhesions of the tumor mass were broken up, both cysts being ruptured by the process of enucleation. The cysts contained a thick chocolate-colored fluid. The uterus, both tubes, and ovaries were removed. Dr. Studdiford believed that one of the cysts had ruptured as a result of the examinations made during the two weeks prior to the operation.

The specimens consist of the whole uterus, with both tubes and ovaries. The fundus and posterior surface of the body of the uterus are almost completely covered by shaggy adherent masses of brownish-red material having the appearance of organizing blood clots. The uterus otherwise appears practically normal.

Adherent to the surfaces of the tubes are several brownish-red masses varying from 1 mm. to about 10 mm. in diameter. Some of these are sessile, others pedunculated; the surfaces are generally smooth. The fimbriated extremities appear normal.

Each ovary contains a single large cyst. The cysts, which have been ruptured and evacuated, are quite similar in appearance and size, measuring about 8 cm. in diameter. On the peritoneal surfaces are numerous small flattened nodules, varying from a dark brownish-red to a pale yellow color. Portions of the surfaces are also covered by patches of a thin membrane of similar material. The walls of the cysts are firm whitish tissue from 1 mm. to 3 mm. in thickness. The linings are partly smooth and white, but for the most part are covered by slightly roughened patches of rusty brown material. Near the hilum of each ovary the walls are thicker, and in the left ovary are two small cysts with rough brownish lining, and also a large Graafian follicle.

Microscopic Examination. Ovaries: The cysts are lined in part by a single layer of non-ciliated columnar epithelium. At several points small epithelial-lined pockets or glands penetrate the cyst wall a short distance. None of these structures present a definite resemblance to endometrium. Where the linings of the cysts are devoid of epithelium they consist partly of rather dense fibrous connective tissue containing moderate numbers of lymphocytes, and scattered phagocytes containing granules which give the staining reaction for iron, and are evidently hemosiderin. In many other places the inner layer of the cyst wall is made up of aggregations of peculiar large cells with relatively small vesicular nuclei. The largest of these cells are frequently multinucleated. In sections stained with hematoxylin and eosin the cytoplasm usually appears homogeneous and has a waxy-looking, neutral, grayish color. Some of the cells are finely granular or vacuolated, and many contain granules of brown pigment. (Sampson calls these cells "endothelial leucocytes." So far as I

have been able to determine, they appear, rather, to develop from connective tissue cells or stroma cells in the cyst wall. Sampson noted their resemblance to lutein cells.) A staining reaction for hemofuscin was carried out according to the method recommended by Mallory, Parker, and Nye.⁹ This differentiates the hemofuscin as bright red granules, while hemosiderin is unstained. This method shows a large proportion of the above-mentioned cells packed with fine granules of hemofuscin, while they contain only a small amount of hemosiderin. Many of the cells also contain numerous fine fat droplets, as shown in frozen sections stained by Sudan III.

The nature of the "chocolate" material contained in the cysts is indicated by small portions of it which are retained in several pockets or recesses in the cyst wall. Several of these diverticula near the hilum of the ovary are quite deep and branching. They are filled with pigment particles, varying from minute granules to round masses three or four times the diameter of a red blood cell. Many of the granules are grouped in large masses which are surrounded and held together by a narrow layer of homogeneous non-pigmented substance which has the appearance of a capsule. (See Fig. 1.)

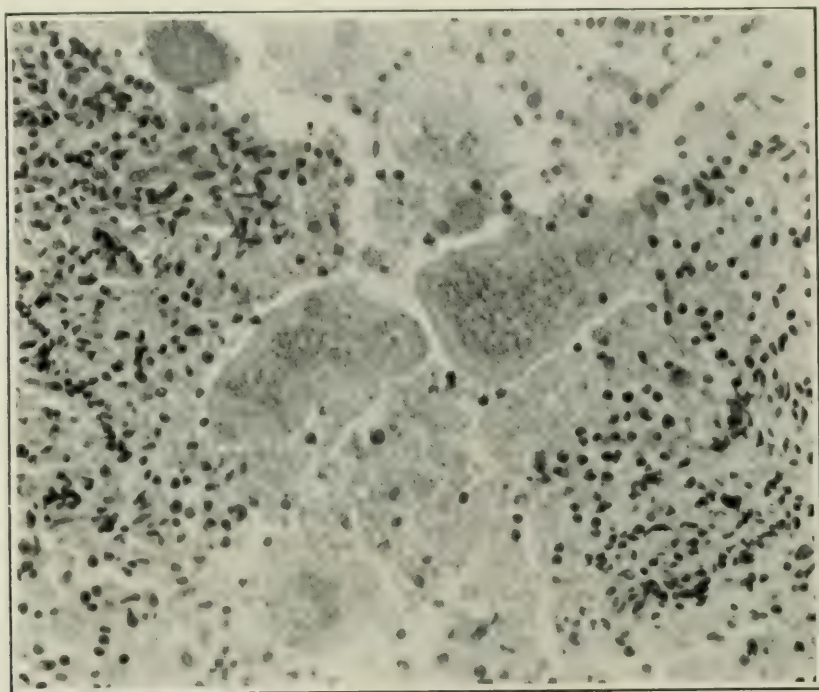


FIG. 1. Masses of pigment lying in recess communicating with cavity of cyst. Each mass is surrounded by a narrow layer of homogeneous non-pigmented material.

In sections stained with eosin the color of the pigment varies from yellow to a bright orange. Some of the granules give an atypical reaction for hemofuscin. The iron reaction is negative.

The walls of the recesses communicating with the cyst cavity are made

up of great numbers of large cells of the type already described, containing hemofuscin granules, fat droplets, and a small amount of hemosiderin. In addition to the phagocytosis of small granules of pigment by individual cells, large masses are partly or completely surrounded by groups of phagocytes which appear to be wandering out from the cyst wall. In the deeper layers of the wall, external to the zone of large cells, there are abundant deposits of hemosiderin.

Several spots in the lining of the cysts show recent hemorrhage, but the material contained in the cysts appears to consist mainly of old pigment in which but few well-preserved red corpuscles can be recognized.

Uterus and Fallopian tubes: These are normal except for changes on the peritoneal surfaces.

Peritoneum: Sections of the reddish-brown masses of tissue adherent to the surfaces of the ovaries, tubes, and uterus show them to be composed chiefly of closely packed large mononuclear cells and multinucleated giant cells. In the superficial layers of these nodules are embedded numerous masses of pigment which take a bright orange color in sections stained with hematoxylin and eosin. (See Fig. 2.)



FIG. 2. Pigment masses embedded in nodule on peritoneal surface of ovary

These masses of pigment correspond in size, shape, and structure to those seen in the cyst contents. Most of them are surrounded by the same homogeneous non-pigmented layer or capsule. The pigment does not give a reaction for iron, and only a few of the granules in the masses give an atypical reaction for hemofuscin.

These peculiar bodies are in various stages of encapsulation and digestion by giant cells. In all of the peritoneal nodules the picture produced by the presence of great numbers of giant cells is very striking. (See Fig. 3.) In the deeper portions of the nodules many of the giant cells contain only a few scattered granules of pigment, some of which give a reaction for hemofuscin. Many of the mononuclear cells are filled with hemofuscin granules, but hemosiderin is much less abundant.

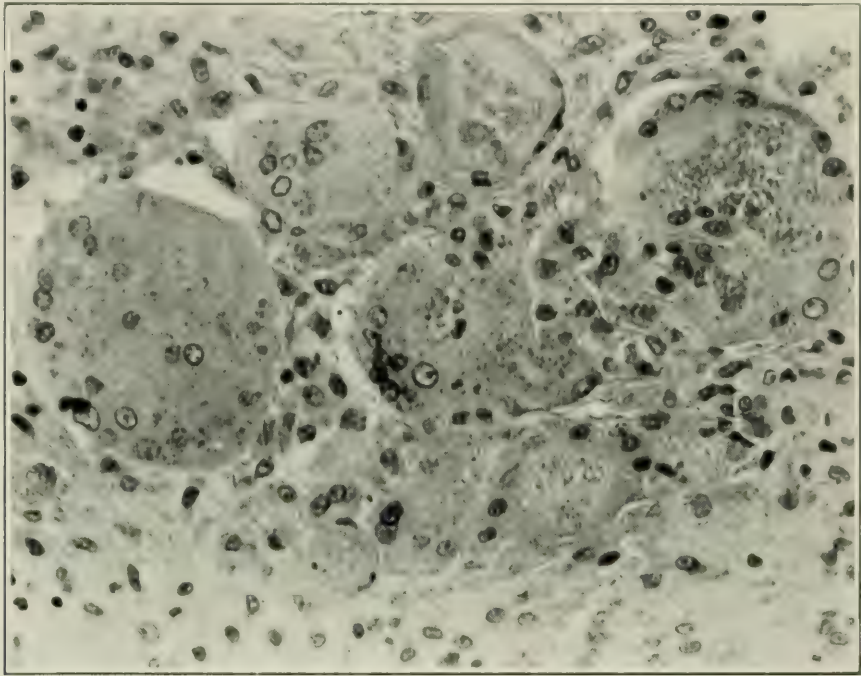


FIG. 3. Giant cells in nodule on peritoneal surface of Fallopian tube. Shows various stages of encapsulation and digestion of masses of blood pigment.

In sections of the posterior surface of the uterus there are several irregular glands lined by columnar epithelium. These penetrate a short distance between the muscle bundles. They are not surrounded by cells like those of the stroma of the endometrium.

The mesothelial cells of the peritoneum covering the Fallopian tubes are in many places thickened to cuboidal or columnar form. This occurs especially in depressions between folds or where the surface is covered by unorganized masses of pigment. On the peritoneal surfaces of the ovarian cysts are several small gland-like structures which are evidently pockets of serosa.

It seems evident that a considerable proportion of the "chocolate" material discharged from the ruptured cyst into the peritoneal cavity consisted of pigment granules clumped in large masses. Countless numbers of these calculus-like masses pro-

duced an irritative and proliferative reaction in the peritoneum with the resulting formation of nodules of tissue in which the coarse particles became embedded. The reaction was probably due to mechanical stimulation rather than to the chemical nature of the pigment. The mode of formation of these concretions is not wholly clear. The most plausible explanation seems to be that they are masses of pigment which, lying in or along the lining of the cyst, have been surrounded and cemented together by phagocytes.

This case has not furnished a sufficient basis for entering into a discussion of the theory of epithelial implantation, but it is certain that changes in the morphology of the peritoneal serosa can produce structures practically indistinguishable from epithelial glands.

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Discussion:

DR. MACNEAL: It is an interesting question to decide whether such structures have arisen by metaplasia or by displacement.

DR. WOOD: It seems to me that one is not safe in assuming that these are transplants from the tube or uterus unless the cells are ciliated. Certainly all sorts of cellular peritoneal reactions and remarkable glandular structures are found which are evidently due to downgrowth of the serosa cells, and unless that can be shown, it seems to me that Sampson has a long way to go to prove that these are all implantations. Dr. Johnson's pictures look like what would be expected from a serosal reaction in the peritoneal cavity, and I assume he interprets it in that way.

DR. JOHNSON: As regards the serosal reaction, I felt at first convinced that Sampson was dealing with a reaction of the serosa, but since I have seen the photomicrographs in his articles and an almost identical reproduction in many of these of the structure of endometrium, and as he states that the epithelium is sometimes ciliated, it seems to me that he is getting the best of

the argument. As to his theory that these structures are due to implantation of fragments of endometrium which have escaped from the fimbriated extremity of the tube, I think that is more difficult for him to establish, and he does not claim to have proved it in any case, but he believes that he can differentiate two different types of these implantations, one resembling endometrium of the uterus, and one the mucosa of the Fallopian tube. Those derived from the latter are more frequently ciliated than those which he thinks are derived from the endometrium. He also believes that it is possible that other cystic growths and carcinomata of the ovary may arise from such implantations.

A CASE OF MALTA FEVER OF AMERICAN ORIGIN

G. JARVIS COFFIN, M.D., AND L. W. FAMULENER, M.D.

Malta, Mediterranean, or undulant are terms commonly applied to designate a fever associated with a specific infectious disease, which has probably existed in the Mediterranean littoral for centuries. In the more recent past it has been confused with malarial and typhoid fevers, since its clinical aspects show characteristics of both of these diseases, in particular the latter. Bruce, in a study of the disease in 1887, succeeded in isolating an organism from the spleen of a patient dead of Malta fever, which he called *Micrococcus melitensis*. Since then this organism has been frequently cultured from the blood and urine of cases of the disease, and is considered to be the true etiological factor. Other workers have succeeded in isolating similar organisms from patients suffering from fevers exhibiting the same clinical symptoms, but these organisms varied in their agglutinating and absorption characteristics when tested with specific sera produced by immunization with the true *M. melitensis*. Such organisms have been called *M. pseudo-melitensis*, and *M. para-melitensis*. Apparently Malta fever embraces a group of infections produced by very closely related organisms with a parallelism similar to that of the enteric group of fevers, following infection with either *B. typhosus* or one of the *B. paratyphosus* organisms. A Committee appointed in 1904 by the British Government for the study of Malta fever discovered that the specific organism occurred both in the blood stream and the milk

of goats, the milk being the principal source of infection to man, through its use in a raw condition as a food. Quite a large percentage of the goats on the Island of Malta at that time were found harboring the organism, apparently without being injuriously affected. By prophylactic measures, such as either discontinuing the use of, or boiling the milk, and the elimination of affected animals, the incidence of the disease rapidly decreased on the island. However, other modes of spreading the infection are possible. In particular, contact infection may occur among careless attendants, since the organism is eliminated in considerable numbers in the urine of the patient. Also exclusive of ingestion of the organism, infection may occur by inhaling contaminated dust, or through skin abrasions.

The distribution of the disease has become generalized. Endemic centers have been discovered in each of the continents and Oceanica. It occurs in the tropical, subtropical, and temperate zones, and probably has existed for many years in Texas where it was known as "slow fever." The first American case reported as originating in the United States was presented by Colonel C. F. Craig, U. S. A. Medical Corps, in 1905. Ferenbough in 1911 reported five cases occurring in Texas, all of which had worked with goats and had drunk goats' milk. Shortly afterward tests were made on 125 goats, and 19.4 per cent. were found infected. Since then, from time to time, cases have been reported from various portions of southwestern United States. In the summer of 1922 the first outbreak of Malta fever to occur in any city in the United States was in Phoenix, Arizona. The outbreak resulted from the sale of goats' milk from a high class dairy.

D. S., at present a patient in St. Luke's Hospital, recently returned from Phoenix, and gave a history of drinking goats' milk purchased from that dairy. At the time there must have been some suspicion of the goats' milk being infected, for our patient was told that the dairy was being blacklisted. Lake has made an extensive study of this epidemic and reports it in the U. S. Public Health Service Bulletin of November, 1922.

Symptomatology: The period of invasion is ten to fourteen days, and is characterized by chills, general malaise, muscular pains, insomnia, and general depression. The temperature rises by step-like elevations, reaching a higher point each successive evening, and falling a little each morning.

D. S., with a history of six weeks' illness, was admitted on March 27th, with a temperature of 98.6, pulse of 88, respirations 20. That evening his temperature rose to 101.6, falling to 99.1 the following morning. He had just returned from a long visit in Phoenix, Arizona, where he had first noticed slight generalized abdominal pain, and had been constipated. A brisk purge seemed to relieve him for a day or two, but soon his temperature gradually became higher, reaching its peak usually by eight o'clock in the evening. The highest fever was 103.4. In the morning the temperature was usually 98 or 99. He had had a fair appetite, no nausea, no vomiting, no diarrhoea, no cough nor hemoptysis, but he did complain of having severe night sweats, which still persist. No symptoms referable to the cardiovascular system had been noticed, but he did complain of vague joint and muscular pains, particularly in the evening, about the time his temperature was at its highest. There was considerable prostration. In the eight weeks previous to admission he had lost twenty pounds in weight.

Physical Examination: The patient was a fairly well-nourished, well-developed, white male about thirty-five years of age, who appeared chronically ill.

The eyes, ears, and nose were negative. The upper teeth were all extracted. The tongue was coated with a light brown coating. The pharynx was somewhat red and injected. The neck was apparently normal except for enlargement of the posterior cervical lymph nodes.

There was a generalized glandular enlargement, although not marked; the axillary, cervical, epitrochlear, and inguinal glands were all palpable.

The lungs were negative throughout.

Examination of the heart showed the apex in the fifth interspace, 12 cm. from the midsternal line. There were no signs of cardiac hypertrophy or displacement by percussion. On auscultation, the heart sounds were distant and indistinct; there was a soft, blowing systolic murmur at the apex, not transmitted to the axilla or back.

The abdomen was normal in contour, showing no rash nor scars, no "rose spots" nor petechiae. There was generalized abdominal tenderness on deep palpation; the spleen was definitely palpable, but not greatly enlarged. The liver and kidneys were not felt.

The extremities were negative; the reflexes were active and equal; no pathological reflexes were obtained.

The pulse was of fair force, regular, of normal rhythm, with no dichrotism.

Diagnosis: In considering the diagnosis of the patient, the first condition thought of was typhoid fever because of his general appearance, that of a chronically ill person with persistent

temperature; low white blood count, and palpable spleen. However, we were able to rule out typhoid fever on a negative blood culture, Widal, stool, and urine examinations.

The second condition considered was malaria, which was likewise ruled out on blood negative for *plasmodium malariae*.

Because of the patient's general condition, his slight cough, his general glandular enlargement, and the afternoon temperature followed by drenching night sweats, tuberculosis had to be excluded. This was possible by virtue of his negative sputum for tubercle bacilli, the absence of physical signs in his lungs, and the negative x-ray report.

It was evident that the patient was suffering from a prolonged blood infection, and because of the slight murmur of mitral insufficiency heard at the apex, subacute malignant endocarditis was considered. The patient had no petechiæ, no other evidences, either from his history or physical examination, of a cardiac condition, and blood cultures were negative for the usual infecting organisms of a malignant endocarditis.

Several other conditions were considered as possibilities, but in each case the diagnosis was not sustained by laboratory or physical findings. While casting about for a suitable diagnosis, the patient was more closely interrogated regarding his recent activities. It was during this time that the history of his drinking goats' milk in Arizona came to light. He said he had been told that the goats' milk was infected, but did not know with what disease. Malta fever was suspected, and with such a lead the serum was sent to Washington for tests against *B. melitensis*, which proved to be the correct diagnosis.

Laboratory Examinations: On admission, March 27, 1923, the red blood cells were 4,600,000; hemoglobin, 93 per cent.; white blood cells, 10,300; polymorphonuclear leucocytes, 60 per cent.; lymphocytes, 40 per cent. Counts were made every few days, which showed little variation. The last examination showed red blood cells, 4,700,000, and hemoglobin, 88 per cent.

Inoculations of the freshly withdrawn blood were made in both plain broth and dextrose broth flasks, and platings were made with plain nutrient agar, dextrose agar, and sodium glycocholate agar (when typhoid fever was suspected). On March 27th, the cultures on blood agar plates showed only one colony of a minute Gram-negative organism which resembled *B. influenzae*. Broth cultures on the sixth day showed cloudiness, but no organism was re-

covered in transplants. On March 30th, second cultures failed to show any growth other than a diphtheroid (contaminant?) which appeared on one of the plain broth flasks on the fifth day. On April 9th, the third culture showed minute colonies, few in number, on the blood plates towards the end of the first week; also a small Gram-negative coccoid organism developed about the same time, both in plain and dextrose broth. These organisms by cultural tests as well as morphological and staining characteristics resembled *B. melitensis*.

A blood smear examined on April 28th showed no malarial parasites.

On April 13th a blood sample was taken to determine the presence of specific agglutinins (*B. melitensis*). The serum was separated and sent to the Hygienic Laboratory, Washington, D. C., to be tested against *B. melitensis*, as no culture of this organism was available (New York City Health Department Laboratories). Later, Dr. McCoy, Director of the Laboratory, reported that the serum strongly agglutinated the *B. melitensis*. Further serological studies were carried out by one of us, which will be discussed below.

Chemical analysis of the blood showed it to contain 20.7 mg. of urea nitrogen per 100 c.c.

The Wassermann reaction on March 30th, and on April 10th, was negative, both with cholesterinized and acetone-insoluble antigens.

The Widal reaction on March 28th showed no agglutination with *B. typhosus*, *B. paratyphosus A*, nor *B. paratyphosus B*.

Cultures were made of the duodenal contents on March 21st, which developed *staphylococcus albus* and *streptococcus viridans*.

A lumbar puncture performed on April 8th gave the following results: The count was five small lymphocytes to the c.mm., and the colloidal gold curve, the globulin test, and the Wassermann reaction were all negative.

The sputum showed no tubercle bacilli.

Bacteriological examination of the stool on March 28th and 30th showed no *B. typhosus*. It was negative for blood by the guaiac test on March 28th.

Bacteriological examination of the urine on March 28th showed no *B. typhosus*, but *B. coli communis* developed. On March 30th the urine again was negative for *B. typhosus*. On April 12th a Gram-negative coccoid organism developed from a voided specimen when cultured on the usual media, but was not isolated from the contaminants present. On April 17th a catheterized specimen was inoculated in plain infusion broth and 5 per cent. glycerin infusion broth. A culture from the glycerin broth yielded a minute Gram-negative coccoid organism which on plating on lactose litmus agar yielded colonies which corresponded to those of *B. melitensis*.

Repeated chemical examinations gave negative tests for albumin, sugar, diacetic acid, and indican.

I. *Clinical.—Duration:* The average duration of illness is three months, but some cases last as long as a year.

There are four varieties: (1) the typical form, as described; (2) the malignant type, in which soon after the patient is taken ill, the typhoid state supervenes and death occurs from cardiac

failure in one to three weeks; (3) the intermittent type, slow in onset, mild in course, the patient complaining usually only of general malaise, nervous irritability and night sweats. Its duration may be a few weeks to six months; (4) the ambulatory form, which is more benign than the intermittent type. The sufferer may show no symptoms at all or may complain of weakness and slight feverishness.

Complications are rare; orchitis is the most common; pneumonia may occur; also occasionally ulcers in both large and small intestine which may give rise to hemorrhage.

The prognosis is good; the disease rarely proves fatal, the death rate being 2 per cent. Burt and Lamb attribute a certain amount of prognostic value to the agglutination test, and regard persistent low agglutination as a bad sign.

In considering the treatment, general measures are those applied to any patient with a persistent temperature. For high fever cold sponging is recommended; attention to the bowels is highly important. Drugs seem to be of little value, except symptomatically. Large doses of quinine, thymol and calomel have been advocated, but have not proved efficacious. Anti-melitensis sera have been tried, but have been found disappointing. Vaccines are recommended in protracted cases with high fever by some authors. Autogenous vaccines may be prepared and given in doses of 100 to 500 millions subcutaneously, or intravenously in doses of 20 to 60 millions. Change of climate has been advocated, especially the higher altitudes.

2. *Bacteriological*: More recent studies upon the specific organism causing Malta fever show that it should be classed with the bacillary types rather than as a micrococcus, and the designation *Bacterium melitensis* is now employed by most bacteriologists. Its measurements as given by different authorities vary. Meyer states that its length varies between 0.4 to 2.2 microns and the width between 0.4 to 0.8 micron, while others give more limited measurements, in particular, for the length. Much depends upon the age of the culture and the medium upon which it is cultivated. The minute organism may appear singly, in diplo forms, or show a tendency to short chain formation, in which

case it appears coccus-like. It is considered non-motile by most writers, while others ascribe motility and the presence of flagella, but later studies do not support this claim. Kendall states that indol or other decomposition products of the aromatic amino-acids have not been found in cultures; it does not produce proteolytic enzymes, nor does it produce either acid or gas in any sugar; therefore it is culturally inert. By the Gram-staining method it is found to be negative. The organism is recognized by the above morphological, staining, and cultural characteristics. However, Evans first called attention to the fact that *Bacterium abortus* (Bang), which is responsible for infectious abortion in domesticated animals, also possesses like characteristics, and so closely resembles *B. melitensis* that cross agglutination with the respective specific sera may occur to a considerable extent. This introduces the question whether cases from whom such an organism has been isolated are infected with *B. melitensis* or *B. abortus*. But to the writers' knowledge, no authentic case of generalized infection (septicemia) due to the *B. abortus* is on record. Still the interesting possibility of such an infection must be considered.

It is not necessary to detail the cultural characteristics of *B. melitensis* on the various media, as they are adequately dealt with in the standard text-books of bacteriology. But it is well to bear in mind that the organism occurs only in small numbers in the blood stream in the acute stage of the disease, and in blood cultures develops very slowly. In our case the colonies first appeared on the poured agar plates several days after culturing the blood. Then only a few, very small, translucent, slightly elevated, round colonies appeared. We only succeeded in getting the organism in blood culture on the third attempt, at which time the true character of the disease was suspected and the organism was especially sought by taking the culture as the fever was rising to its height in the late afternoon. It is possible that the organism developed in small numbers in the earlier blood cultures, but the minute colonies were not recognized in the course of the routine examination. As to the question of selective media, none seemed to possess particular advantage over another. Our best growths appeared on 5 per cent. human blood agar

slants, 5 per cent. glycerin agar, and 1 per cent. dextrose; the solid medium seemed better than the broths. The most favorable reaction of the medium lies perhaps between pH 7.2 and 7.4. Cultures of catheterized specimens of urine in relatively large amounts in 5 per cent. glycerin infusion broth gave positive results. An extensive series of cultural tests were carried out on various media, the results of which confirmed the observations of other workers on this organism.

3. *Serological*: In the diagnosis of Malta fever, the serological tests are important, as agglutinins appear in considerable amounts in the blood quite early in the disease. As previously noted, when the true character of our patient's disease was first suspected, a sample of his serum was sent to the Hygienic Laboratory, Washington, for serological examination. It was found to strongly agglutinate the melitensis organism. Later we not only succeeded in culturing the organism from the blood and urine of the patient, but we were able to procure two laboratory strains (No. 2 and No. 20) of *B. melitensis*. Unfortunately, the histories of the latter strains were not obtainable, but probably they had been under artificial cultivation for a long period since isolation. Also, through the kindness of Dr. Charles Krumwiede of the New York City Health Department Laboratories, we were supplied with specific agglutinating serum from animals which had been immunized against each of the above laboratory strains of *B. melitensis*. Therefore, we were enabled, through the above resources, to test not only the agglutinating properties of the patient's serum against other strains of the organism, but also to test the strains isolated from the blood and urine against known specific melitensis sera. A series of agglutination tests was made by using the patient's serum in various dilutions (physiological salt solution) with broth cultures of the organisms originally isolated from his own blood stream, and from the urine. It was found that a dilution of 1:200 of the patient's serum, when added to an equal volume of a forty-eight-hour broth culture of the organism, either from his own blood, his urine or the two laboratory strains, produced a good agglutination reaction in hanging drop, after standing one hour at

room temperature. Both of the specific agglutinating sera of animals immunized against laboratory strains of *B. melitensis* gave good agglutination reactions in dilutions of 1:300, with organisms isolated from the patient's blood stream, and from the urine; one of the sera (No. 20) gave even a slightly higher agglutination value with the urine organisms, although this might have been due to variations in the cultures, as forty-eight hours' incubation was necessary for sufficient growth for the test. One of the sera gave a fairly good agglutination of the two laboratory strains in a dilution of 1:400, while the other serum gave a similar agglutination of the same organisms in a dilution of 1:500. Apparently the two laboratory strains belonged to the same subgroup of *B. melitensis*. The results of the direct and the cross-agglutination tests, as indicated above, furnish important confirmatory evidence as to the nature of the specific infecting organism—*B. melitensis*—in the case under observation. Series of "agglutinin absorption" tests between patient's serum and the cultures of *B. melitensis* described, and between the specific melitensis immune sera and the organisms derived from the patient's blood, and from the urine, were carried out. The results of the agglutinin absorption tests also supported the correctness of the diagnosis of an infection due to *B. melitensis* in this case.

In conclusion, we wish to acknowledge our indebtedness to Dr. G. W. McCoy,* Director of the Hygienic Laboratory, Washington, for coöperation in laboratory diagnosis, and to Dr. Charles Krumwiede of the Bureau of Laboratories, Department of Health, New York City, for specific sera supplied for our studies. Also to Miss Julia Hewitt and Miss Ruth Kautsky for technical assistance in the course of the laboratory studies.

* Since presentation of the above paper, a report upon cultures from the above case has been received from Dr. McCoy, to the effect that the organism was found to correspond with the serological type found in the vicinity of Phoenix.

A STUDY OF A MONILIA ISOLATED FROM A CASE OF SPRUE

JULIA A. W. HEWITT, B.A., AND L. W. FAMULENER, M.D.

The symptom-complex commonly known as tropical sprue or psilosis is generally recognized by most authorities on tropical medicine as constituting a definite disease entity. The disease exhibits as its chief clinical manifestations the following symptoms: stomatitis, with marked ulceration of tongue and buccal mucosa; copious, frothy morning stools, characterized by acid reaction, offensive odor, and the presence of much unabsorbed fat; nervous and physical depression; wasting and anemia. The onset is insidious, and the disease tends to run a chronic course, with a tendency to relapse with alternating remissions which may continue for a number of years.

In its geographical distribution it is mostly confined to tropical and subtropical countries, although it may be endemic in certain localities in the temperate zone. It is found in particular in South China, Korea, East Indies, Ceylon, India, tropical Africa, West Indies (Porto Rico, Cuba), and probably in our southern states to a limited extent.

The etiology of this disease is of special interest. Some authorities state that its cause is unknown, while others take a decided stand, maintaining that it is a specific infectious disease. As a result of the rather obscure origin of the disease, many theories have been advanced by various observers to solve the question of etiology. Chief among these are:

- (1) Exhaustion of certain physiological functions, in particular, that of the pancreas.
- (2) Deficiency of certain essential food elements.
- (3) Intestinal parasites.
- (4) Infectious agents, either bacterial or of the higher forms, such as yeast-like organisms or fungi. The latter group of infectious organisms (*Monilia*) is the one in which we are more interested since at the present time it receives more accept-

ance as a probable etiological factor. The *Oidium* or *Monilia* theory was first advanced by Kohlbrugge in 1901. In his study of the disease in Java he found present in the digestive tract of his cases an organism which he decided was *Oidium* (*Monilia*) *albicans*. In a fatal case it was found that the fungus had invaded the deeper strata of mucosa and submucosa of the tongue, the glands, etc. Other observers soon confirmed his findings. Castellani, in his studies upon sprue, also reported the presence in his cases of a number of species of monilia, which he did not consider as the primary cause of the disease, but he recognized their significance in causing some of the important symptoms of the disease (frothy stools). Later, Bahr in a series of studies supported Kohlbrugge's theory. But perhaps the studies of Ashford upon the etiology of tropical sprue in Porto Rico have supported the *Monilia* theory more than any other recent investigation. He finds almost constantly in the digestive tract of his cases a monilia which he calls *Monilia psilosis*, and he considers it the specific cause of the disease. In a recent publication he defines the disease as follows: "Sprue is a specific mycosis of the digestive tract, due to the colonization of *Monilia psilosis* therein, generally limited to tropical and subtropical lands, and usually, although not always, superimposed upon a state of glandular insufficiency, often the sequela of a chronic deficiency in food elements necessary to perfect nutrition" (*Oxford Medicine*).

The *Monilia psilosis*, as described by him, appears in unstained preparations as round, glistening bodies from three and a half to five micra in diameter. The limiting membrane is clearly defined, the cell "contains one or more fairly large, highly refractile bodies, a large, faint vacuole and, often, minute, violently motile, filiform bodies. Reproduction is by gemmation or by side-budding from hyphæ or chlamydospores. The mycelium develops late in favorable, early in unfavorable media, and consists of jointed hyphæ, whose articles give the appearance of a split bamboo pole containing a chain of brilliantly refractile fat globules." When cultured upon the surface of poured plates, using Sabouraud's 4 per cent. glucose agar (reaction + 2), the colonies appear after three or four days as

convex, almost hemispherical forms, with sharply defined margins, are soft, and of a creamy white color. In old agar slant cultures, a mossy undergrowth of the mycelia may be observed.

Ashford places much stress upon and holds as characteristic and very important gelatin stab cultures of this organism. The growth occurs along the puncture line with arborescent extension of mycelia in the upper portion giving an "inverted pine-tree" appearance. The gelatin is not liquefied. Also litmus milk is rendered alkaline but not coagulated. When the various sugar media are inoculated he finds that "acid and gas are produced in glucose, levulose and maltose and, in about one third of the strains, in saccharose and galactose. None of the other sugar bouillons are thus affected, but tend to become steadily more and more alkaline." As is apparent, Ashford is able rather sharply to differentiate the particular monilia which he considers the direct cause of sprue, from other yeast types which may appear in the stool, and thus offers a guide to other investigators in their studies along similar lines.

Since the writers have had an opportunity to study a case recently admitted to one of the wards of St. Luke's Hospital, clinically diagnosed as tropical sprue, an investigation was undertaken along the laboratory lines as suggested in the publications of Ashford. We shall not attempt to go into the clinical history of this case other than to state that the patient came from Louisiana, but had formerly lived in Haiti. The patient was under observation a number of weeks, during which time the diagnosis of sprue was established, but in spite of all treatment eventually succumbed to the disease, with certain complications. An autopsy was performed which afforded material for further laboratory studies. This report will be confined to the mycological studies upon the *Monilia* isolated.

During the period while the patient was under observation, repeated examinations of the stool by culturing on various media, including dextrose broth and Sabouraud's maltose agar plates, showed no monilia. But scrapings taken from the inflamed, fissured tongue, and the duodenal contents, when cultured by special methods, yielded monilia. The monilia isolated from

both sources appeared, by cultural and fermentation tests, to be of one species only. At autopsy several weeks after the monilia was isolated from these sources, scrapings were again made from the tongue, and materials were taken from the duodenum and colon for culture. In each case a monilia was isolated, and showed the same cultural characteristics as those previously isolated from the tongue and the duodenal contents. The cultural and fermentation properties of these organisms were carefully studied, and the results were compared not only with the published data of Ashford, but also with three strains of *Monilia psilosis* which were supplied to us by Dr. McCoy, Director of the Hygienic Laboratory, Washington.

It is interesting to note at this point that each of the three strains which Dr. McCoy informs us originally came from Porto Rico six or seven years ago, gave in each instance different fermentation reactions on the various sugar media employed. Since Ashford states that "aberrant types of *Monilia psilosis* may be reinvested by animal passage with their cultural characteristics" we successively passed each strain through three guinea pigs in order to determine if each of these stock strains might by such a procedure be brought into closer conformity. In each instance it was found that the cultural characteristics remained unchanged from those originally present before animal passage. The strain which we isolated from our case corresponded quite closely in fermentation properties upon carbohydrate media with one of the Hygienic Laboratory strains (No. 203), and with *Monilia psilosis* strains procured later directly from Dr. Ashford in Porto Rico. The strain which we isolated fermented dextrose, levulose and maltose, producing acid and gas, and galactose, with slight acid and no gas. Lactose, saccharose, and mannite showed no fermentation changes. This organism however did not produce, as did the corresponding Hygienic Laboratory strain, the typical "inverted pine-tree" growth in gelatin, although it did not liquefy that medium. After passage through guinea pigs our strain did not alter its fermentation characteristics, but in two instances the guinea pigs died from intraperitoneal injections of the organism, and on

autopsy showed small yellowish-white multiple abscesses in the body involving even the lungs, which would indicate a septicemia. These abscesses yielded the *Monilia* in pure cultures. As to the importance of the configuration of the growth in gelatin, we are unable to decide, owing to the very limited data supplied by our studies. However, we may state that a monilia isolated from a pneumonic sputum also showed a similar "inverted pine-tree" growth in gelatin without liquefaction of the medium. Otherwise this organism did not correspond with either of the types of *Monilia psilosis* at hand. Also cultures made from compressed yeast cake (bakers') showed two types, one of which likewise produced the "inverted pine-tree" growth in gelatin with no liquefaction of medium, while it did not ferment sugars like the *Monilia psilosis* strains. It would appear from these controls that the "inverted pine-tree" growth of monilia in gelatin without liquefaction is not confined strictly to the *Monilia psilosis*, while on the other hand the absence of such a property on the part of a non-liquefying monilia isolated from a sprue case with fermentation properties corresponding to those of *Monilia psilosis* might be considered a variant, if we are to accept Ashford's conception of the etiology of sprue.

As to the mycelial formation in older cultures upon Sabouraud's agar slants and broth media, we found no such structures on agar slants even after they had developed a heavy growth and had stood at room temperature for a number of weeks. Occasionally they were found in plain infusion broth cultures but almost constantly and in relatively great numbers in cultures upon 4 per cent. glucose infusion broth (adjusted to slight acid reaction). There were present also numerous bizarre forms which Ashford describes in his studies. Such forms were developed especially in the old cultures after they had been kept for some weeks at room temperature.

We do not care to draw any definite conclusions at this time relative to the rôle of monilia in the etiology of tropical sprue, but the results of our study support the findings of Ashford. As the opportunity arises our laboratory investigations will be continued upon other cases of this disease. The results of this

single study upon the associated *Monilia* found in a case of tropical sprue are presented for consideration of others, who may be engaged in similar studies.

Discussion:

DR. MACNEAL: Ashford, of course, is quite convinced that the *Monilia psilosis* which he has described has an etiological relationship to sprue, and I believe his conclusions are based on finding the organism in the stools of patients which he examined in Porto Rico, and also in fairly characteristic results which he can produce in guinea pigs. This work has been substantiated by a considerable amount of serological work by Dr. Michel, of the Public Health Service, in conjunction with Colonel Ashford.

Cases of sprue are nearly all of the chronic, recurrent type, and these cases are occasionally seen in New York. I suppose there must be cases here all the time. I know that down at the Post-Graduate Hospital we see sprue nearly every year, and sometimes two or three cases a year. It occurs in people who have had very good living conditions, but have been in the tropics for a prolonged period of time. Men who have been in China for many years on business, or as missionaries, or in the medical service in the tropics, may suffer from sprue. It is very clearly characterized by its clinical manifestations. In spite of the fact that Colonel Ashford is quite confident of the accuracy of his results I think he is very reasonable in his claims. He is anxious to have someone else make a thorough survey of cases of sprue for this particular organism. Our own experience has led us to believe that *Monilia* can be isolated from cases of sprue without very great difficulty, but the identification of such microbes as the cause of sprue, or with the organism which Ashford has described, offers considerable difficulty. Unquestionably there are variations in these microorganisms, possibly because they actually are of different varieties, and possibly because of their readily changed characteristics, which may appear in different strains and which render their identification difficult. At any rate, we have not yet come to any exact criteria by which they can be recognized with certainty. This is a very important disease, and I think that those who have seen it and have some knowledge of it might help us out by discussion.

SOME OBSERVATIONS ON THE CYTASE OF GUINEA-PIG BLOOD

ADELAIDE B. BAYLIS

According to various textbooks and papers published concerning the complement fixation test, the guinea pig cytase is either procured or preserved in various ways, and the mind of the student is left in some confusion as to which method or methods had best be employed.

Kolmer¹ and Wood, Vogel and Famulener² prefer the animals in a fasting state when bled, while the other authorities seem indifferent on this point. Whitman,³ Marchildon,⁴ Addis,⁵ Bordet and Gengou,⁶ Von Foder,⁷ Domery,⁸ and Citron-Garbat⁹ advocate that the serum be separated at once and kept in that manner, while Craig¹⁰ and Massol and Grysez¹¹ maintain that the cytase gives a better reaction if the blood is allowed to clot and the clot kept in the ice box over night. MacNeal¹² and Park and Williams,¹³ agreeing on the keeping of the cytase on the clot, state that it is only necessary to follow this procedure until ready to use the serum, while Agasse-Lafont,¹⁴ Armand Delelle and Negre,¹⁵ Jordan¹⁶ and Besson¹⁷ make no reference to these points at all. Vernes¹⁸ claims that the results obtained are fundamentally altered by the condition of the guinea pigs, as to their health and fasting conditions, and for this reason has abandoned the hemolytic system altogether. While the present communication is wholly preliminary in nature and makes no pretense to present facts from which any final conclusions may be drawn, an attempt will be made to present the results of a series of tests carried out in the laboratories of the New York Post-Graduate Medical School and Hospital during the winter of 1922-23. Grateful acknowledgement is made to Dr. Adele E. Sheplar for her interest and suggestions in the conduct of the work.

The guinea pigs employed were those furnishing blood for the routine serological work of the laboratory. They are bled repeatedly from the heart under light ether anesthesia, about once every three weeks. For each test the blood of two animals was combined and the mixture divided equally between two Petri dishes, one being placed in the ice box for twenty-four hours, the contents of the other being treated at once. Here it might be well to note the observation that if the clot in both dishes immediately after its formation was broken into very small pieces by the aid of two glass rods, the amount of serum obtained was about one third more in quantity than if the clot were left undisturbed until ready to centrifugalize. This procedure did not alter the quality of the serum obtained. The clot was then

broken up a second time just before centrifugalizing. The serum was obtained from guinea pigs bled after eighteen hours' fasting and likewise from guinea pigs bled an hour after their morning meal of bread and milk. As previously stated, one half of the blood obtained was at once put in the ice box immediately surrounded by water containing cracked ice for twenty-four hours, without centrifugalizing, then centrifugalized, and the serum removed. Half of the serum was then used in the test, the other half replaced at 0° C. for another twenty-four hours and again tested. The other half of the blood obtained was centrifugalized at once and the serum removed, one half of which was placed in cracked ice in the ice box for twenty-four hours and then titrated, the other half was poured into a test tube and kept in a jar of ice for one half hour and then titrated, leaving an interval of scarce an hour between the bleeding of the pig and the titrating of the serum.

The corpuscle suspension was in every case either freshly prepared from blood less than forty-eight hours out of the sheep, or such a suspension preserved in the refrigerator immersed in ice water for a period less than twenty-six hours, between the various tests. It is probable that variation in the resistance of the corpuscles played some part in the results obtained but this variation has not been overlooked in summarizing the results. The primary object in view was to shed light on the following questions, these being the general points of divergence of opinion.

1. Is there an advantage in using the serum of the fasting guinea pig in contrast to the serum of the fed guinea pig?
2. Is there an advantage in keeping the cytase on the clot, rather than separating the serum at once and keeping it in a separate container?
3. Is there an advantage in using the fresh cytase within the hour of obtaining it as contrasted with that which has been kept for a longer interval?

Thirteen test tubes were set up and the constituents distributed as shown below :

TABLE I

Tubes	Hemolysin 1-100	Saline 0.9%	Sheep Corpuscles 1-20	Cytase 1-10
1	0.01 c.c.	0.5 c.c.	0.2 c.c.	0.1 c.c.
2	0.02 c.c.	0.5 c.c.	0.2 c.c.	0.1 c.c.
3	0.03 c.c.	0.5 c.c.	0.2 c.c.	0.1 c.c.
4	0.04 c.c.	0.5 c.c.	0.2 c.c.	0.1 c.c.
5	0.05 c.c.	0.5 c.c.	0.2 c.c.	0.1 c.c.
6	0.06 c.c.	0.5 c.c.	0.2 c.c.	0.1 c.c.
7	0.07 c.c.	0.5 c.c.	0.2 c.c.	0.1 c.c.
8	0.08 c.c.	0.5 c.c.	0.2 c.c.	0.1 c.c.
9	0.09 c.c.	0.5 c.c.	0.2 c.c.	0.1 c.c.
10	0.1 c.c.	0.5 c.c.	0.2 c.c.	0.1 c.c.
11	0.2 c.c.	0.6 c.c.	0.2 c.c.	—
12	—	0.6 c.c.	0.2 c.c.	0.2 c.c.
13	—	0.8 c.c.	0.2 c.c.	—

The tubes were thoroughly agitated and incubated one half hour at 37.5° C. in air, meanwhile being thoroughly shaken a second time after fifteen minutes' incubation. Tubes 11, 12, and 13 represent respectively the hemolysin control, the cytase control, and the corpuscle control.

The results obtained are shown in the tables.

Obviously such experimental results can not be properly contrasted without reserve, because of the presence of uncontrolled variables, the influence of which can be measured or overcome only by the statistical analysis of an accumulation of more abundant observations in the same categories. For example, it would appear that the animals bled on December 20, 1922, yielded a relatively poor initial serum, possibly because of some disturbance of health of one or both of the animals. The influence of other uncontrolled variables is strongly suggested by the tabulated data. However, some contrasts in respect to the controlled factors are indicated.

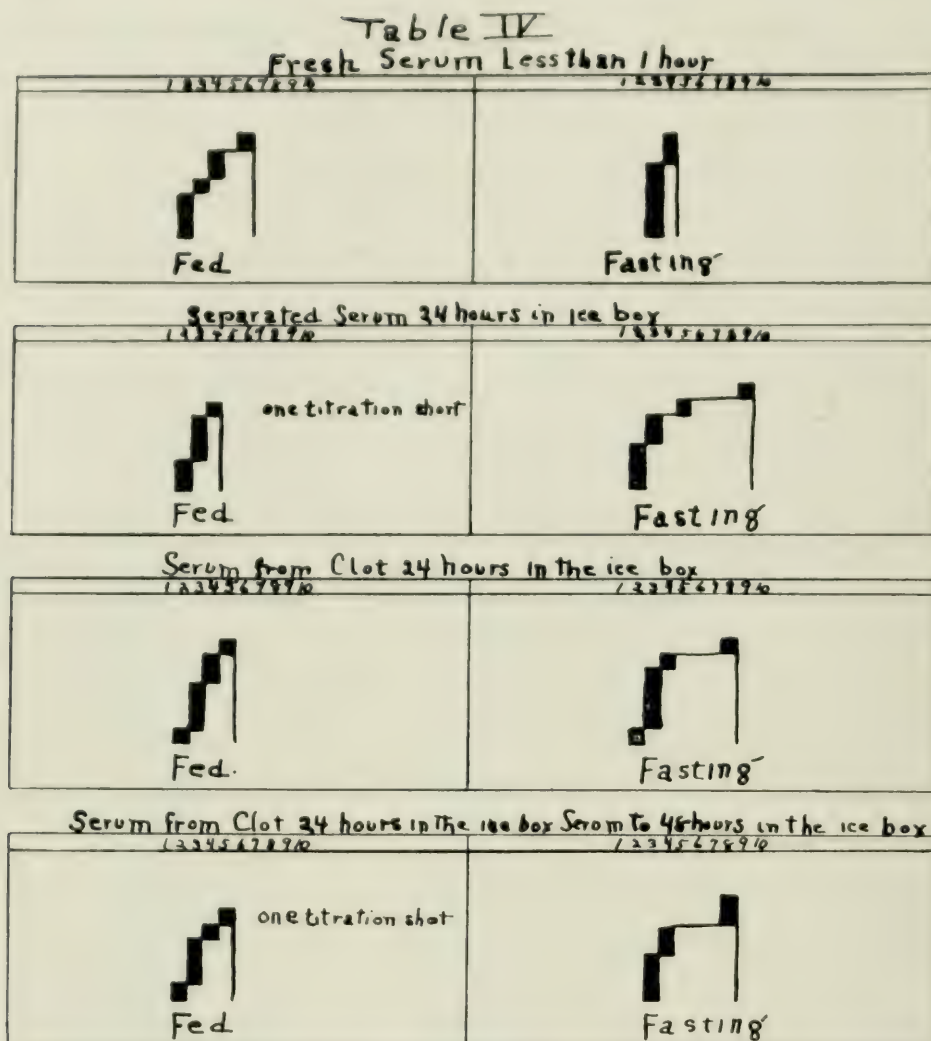
If one regards solely the frequency polygons, it appears that the fresh serum of the fasting animal used within the hour is most constant in its behavior. When kept, however, as separated serum for twenty-four hours or for twenty-four hours on the clot, or for twenty-four hours on the clot and an additional twenty-four hours in a separate container, this serum from the

Table II

Tubes		1	2	3	4	5	6	7	8	9	10	11	12	13
Haemolysin 1-100		0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09	0.1	0.2	—	—
Saline 0.9 %		0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.6	0.6	0.8
Sheep Corpuscles 1-20		0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Cytase 1-10		0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	—	0.2	—
12-18-22 Fed	Fresh serum less than 1 hour	+++	±	—	—	—	—	—	—	—	—	+++	+++	+++
	Separated Serum 24 hours in ice box	(no clot occurred - 5 tubes)												
	Serum from Clot 24 hours in ice box	+++	+++	++	—	—	—	—	—	—	—	+++	+++	+++
	Serum from Clot 24 hours in ice box Serum to 48 hours in ice box	+++	+++	+++	—	—	—	—	—	—	—	+++	+++	+++
12-20-22 Fasting	Fresh serum less than 1 hour	+++	+++	—	—	—	—	—	—	—	—	+++	+++	+++
	Separated Serum 24 hours in ice box	+++	+++	+++	++	+	±	±	—	—	—	+++	+++	+++
	Serum from Clot 24 hours in ice box	+++	+++	+++	++	+	±	±	—	—	—	+++	+++	+++
	Serum from Clot 24 hours in ice box Serum to 48 hours in ice box	+++	+++	+++	++	+	±	±	—	—	—	+++	+++	+++
12-22-22 Fed	Fresh serum less than 1 hour	++	+	—	—	—	—	—	—	—	—	++	++	++
	Separated Serum 24 hours in ice box	+	+	—	—	—	—	—	—	—	—	++	++	++
	Serum from Clot 24 hours in ice box	+	+	—	—	—	—	—	—	—	—	++	++	++
	Serum from Clot 24 hours in ice box Serum to 48 hours in ice box	(growth interrupted)												
12-28-22 Fasting	Fresh serum less than 1 hour	++	±	—	—	—	—	—	—	—	—	++	++	++
	Separated Serum 24 hours in ice box	+++	—	—	—	—	—	—	—	—	—	+++	+++	+++
	Serum from Clot 24 hours in ice box	+++	+	±	—	—	—	—	—	—	—	+++	+++	+++
	Serum from Clot 24 hours in ice box Serum to 48 hours in ice box	+++	+++	+++	++	+	±	±	—	—	—	+++	+++	+++
12-26-22 Fed	Fresh Serum less than 1 hour	++	±	±	—	—	—	—	—	—	—	++	++	++
	Separated Serum 24 hours in ice box	++	±	—	—	—	—	—	—	—	—	++	++	++
	Serum from Clot 24 hours in ice box	+++	±	±	±	—	—	—	—	—	—	+++	+++	+++
	Serum from Clot 24 hours in ice box Serum to 48 hours in ice box	++	±	±	±	—	—	—	—	—	—	++	++	++
1-4-23 Fasting	Fresh Serum less than 1 hour	+++	++	—	—	—	—	—	—	—	—	+++	+++	+++
	Separated Serum 24 hours in ice box	+++	++	—	—	—	—	—	—	—	—	+++	+++	+++
	Serum from Clot 24 hours in ice box	+++	+++	—	—	—	—	—	—	—	—	+++	+++	+++
	Serum from Clot 24 hours in ice box Serum to 48 hours in ice box	++	+	—	—	—	—	—	—	—	—	++	++	++
1-2-23 Fed	Fresh Serum less than 1 hour	+++	++	++	—	—	—	—	—	—	—	+++	+++	+++
	Separated Serum 24 hours in ice box	+++	±	—	—	—	—	—	—	—	—	+++	+++	+++
	Serum from Clot 24 hours in ice box	+++	±	—	—	—	—	—	—	—	—	+++	+++	+++
	Serum from Clot 24 hours in ice box Serum to 48 hours in ice box	++	+	—	—	—	—	—	—	—	—	++	++	++
1-10-23 Fasting	Fresh Serum less than 1 hour	++	±	—	—	—	—	—	—	—	—	++	++	++
	Separated Serum 24 hours in ice box	±	±	—	—	—	—	—	—	—	—	++	++	++
	Serum from Clot 24 hours in ice box	+++	—	—	—	—	—	—	—	—	—	+++	+++	+++
	Serum from Clot 24 hours in ice box Serum to 48 hours in ice box	+++	++	—	—	—	—	—	—	—	—	+++	+++	+++
1-8-23 Fed	Fresh Serum less than 1 hour	++	—	—	—	—	—	—	—	—	—	++	++	++
	Separated Serum 24 hours in ice box	+++	—	—	—	—	—	—	—	—	—	+++	+++	+++
	Serum from Clot 24 hours in ice box	++	++	—	—	—	—	—	—	—	—	++	++	++
	Serum from Clot 24 hours in ice box Serum to 48 hours in ice box	++	++	—	—	—	—	—	—	—	—	++	++	++
1-15-23 Fasting	Fresh Serum less than 1 hour	++	++	±	—	—	—	—	—	—	—	+++	+++	+++
	Separated Serum 24 hours in ice box	++	—	—	—	—	—	—	—	—	—	+++	+++	+++
	Serum from Clot 24 hours in ice box	+++	±	—	—	—	—	—	—	—	—	+++	+++	+++
	Serum from Clot 24 hours in ice box Serum to 48 hours in ice box	+++	±	—	—	—	—	—	—	—	—	+++	+++	+++
1-12-23 Fed	Fresh Serum less than 1 hour	+++	—	—	—	—	—	—	—	—	—	+++	+++	+++
	Separated Serum 24 hours in ice box	±	—	—	—	—	—	—	—	—	—	+++	+++	+++
	Serum from Clot 24 hours in ice box	±	—	—	—	—	—	—	—	—	—	+++	+++	+++
	Serum from Clot 24 hours in ice box Serum to 48 hours in ice box	+++	±	—	—	—	—	—	—	—	—	+++	+++	+++
1-19-23 Fasting	Fresh serum less than 1 hour	+++	++	±	—	—	—	—	—	—	—	+++	+++	+++
	Separated Serum 24 hours in ice box	+++	—	—	—	—	—	—	—	—	—	+++	+++	+++
	Serum from Clot 24 hours in ice box	+++	±	—	—	—	—	—	—	—	—	+++	+++	+++
	Serum from Clot 24 hours in ice box Serum to 48 hours in ice box	++	+	±	—	—	—	—	—	—	—	++	++	++
1-29-23 Fed	Fresh Serum less than 1 hour	+	—	—	—	—	—	—	—	—	—	+++	+++	+++
	Separated Serum 24 hours in ice box	+++	+++	±	—	—	—	—	—	—	—	+++	+++	+++
	Serum from Clot 24 hours in ice box	+++	+++	+	—	—	—	—	—	—	—	+++	+++	+++
	Serum from Clot 24 hours in ice box Serum to 48 hours in ice box	++	+	—	—	—	—	—	—	—	—	++	++	++
1-31-23 Fasting	Fresh serum less than 1 hour	+++	±	—	—	—	—	—	—	—	—	+++	+++	+++
	Separated Serum 24 hours in ice box	++	+	+	±	—	—	—	—	—	—	+++	+++	+++
	Serum from Clot 24 hours in ice box	+	+	±	—	—	—	—	—	—	—	+++	+++	+++
	Serum from Clot 24 hours in ice box Serum to 48 hours in ice box	+++	+	+	—	—	—	—	—	—	—	+++	+++	+++

Table II

Tubes		1	2	3	4	5	6	7	8	9	10	11	12	13	
Hemolysin	1-100	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09	0.1	0.2			
Saline	0.9%	0.5	0.6	0.3	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.6	0.7	0.8	
Sheep Corpuscles	1-20	0.2	0.3	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.5	0.2	0.3	
Cytase	1-10	0.1	0.1	0.1	1								0.2		
Fresh Serum less than one hour	12.18.22	+++	+	-	-	-	-	-	-	-	-	+++	+++	+++	
	12.22.22	++	++	++	+	-	-	-	-	-	-	+++	+++	+++	
	12.26.22	++	+	+	-	-	-	-	-	-	-	+++	+++	+++	
	1.2.23	+++	+++	++	-	-	-	-	-	-	-	+++	+++	+++	
	1.8.23	++	-	-	-	-	-	-	-	-	-	+++	+++	+++	
Fed	1.12.23	+++	-	-	-	-	-	-	-	-	-	+++	+++	+++	
	1.29.23	+	-	-	-	-	-	-	-	-	-	+++	+++	+++	
Fresh Serum less than one hour	12.20.22	+++	+++	-	-	-	-	-	-	-	-	+++	+++	+++	
	12.28.22	++	+	-	-	-	-	-	-	-	-	+++	+++	+++	
	1.4.23	+++	++	-	-	-	-	-	-	-	-	+++	+++	+++	
	1.10.23	+++	+++	-	-	-	-	-	-	-	-	+++	+++	+++	
	1.15.23	++	++	+	-	-	-	-	-	-	-	+++	+++	+++	
Fasting	1.19.23	+++	++	+	-	-	-	-	-	-	-	+++	+++	+++	
	1.31.23	+++	+	-	-	-	-	-	-	-	-	+++	+++	+++	
Separated Serum 24 hours in ice box	12.18.22		(sufficient obtained to allow)												
	12.22.22	+	+	-	-	-	-	-	-	-	-	-	+++	+++	+++
	12.26.22	+	+	-	-	-	-	-	-	-	-	-	+++	+++	+++
	1.2.23	++	+	-	-	-	-	-	-	-	-	-	+++	+++	+++
	1.8.23	+++	-	-	-	-	-	-	-	-	-	-	+++	+++	+++
Fed	1.12.23	+	-	-	-	-	-	-	-	-	-	-	+++	+++	+++
	1.29.23	+++	+++	+	-	-	-	-	-	-	-	-	+++	+++	+++
Separated Serum 24 hours in ice box	12.20.22	+++	+++	+++	++	++	+	+	+	-	-	-	+++	+++	+++
	12.28.22	++	-	-	-	-	-	-	-	-	-	-	+++	+++	+++
	1.4.23	+++	++	-	-	-	-	-	-	-	-	-	+++	+++	+++
	1.10.23	+	+	-	-	-	-	-	-	-	-	-	+++	+++	+++
	1.15.23	++	-	-	-	-	-	-	-	-	-	-	+++	+++	+++
Fasting	1.19.23	++	-	-	-	-	-	-	-	-	-	-	+++	+++	+++
	1.31.23	+	+	+	+	-	-	-	-	-	-	-	+++	+++	+++
Serum from Clot 24 hours in ice box	12.18.22	++	++	++	-	-	-	-	-	-	-	-	+++	+++	+++
	12.22.22	+	+	-	-	-	-	-	-	-	-	-	+++	+++	+++
	12.26.22	++	+	+	-	-	-	-	-	-	-	-	+++	+++	+++
	1.4.23	++	+	-	-	-	-	-	-	-	-	-	+++	+++	+++
	1.8.23	++	++	-	-	-	-	-	-	-	-	-	+++	+++	+++
Fed	1.12.23	+	+	-	-	-	-	-	-	-	-	-	+++	+++	+++
	1.29.23	++	++	+	-	-	-	-	-	-	-	-	+++	+++	+++
Serum from Clot 24 hours in ice box	12.20.22	+++	+++	++	++	+	+	+	-	-	-	-	+++	+++	+++
	12.28.22	+++	++	+	-	-	-	-	-	-	-	-	+++	+++	+++
	1.4.23	+++	++	-	-	-	-	-	-	-	-	-	+++	+++	+++
	1.10.23	+++	++	-	-	-	-	-	-	-	-	-	+++	+++	+++
	1.15.23	+++	+	-	-	-	-	-	-	-	-	-	+++	+++	+++
Fasting	1.19.23	+++	+	+	-	-	-	-	-	-	-	-	+++	+++	+++
	1.31.23	+	+	+	+	-	-	-	-	-	-	-	+++	+++	+++
Serum from Clot 24 hours in ice box	12.18.22	+++	+++	+++	-	-	-	-	-	-	-	-	+++	+++	+++
	12.22.22	++	++	++	+	+	+	-	-	-	-	-	+++	+++	+++
	12.26.22	++	+	+	-	-	-	-	-	-	-	-	+++	+++	+++
	1.4.23	++	+	-	-	-	-	-	-	-	-	-	+++	+++	+++
	1.8.23	++	++	-	-	-	-	-	-	-	-	-	+++	+++	+++
Fed	1.12.23	++	+	-	-	-	-	-	-	-	-	-	+++	+++	+++
	1.29.23	++	++	+	-	-	-	-	-	-	-	-	+++	+++	+++
Serum from Clot 24 hours in ice box	12.20.22	+++	+++	++	++	+	+	+	-	-	-	-	+++	+++	+++
	12.28.22	+++	++	+	-	-	-	-	-	-	-	-	+++	+++	+++
	1.4.23	+++	++	-	-	-	-	-	-	-	-	-	+++	+++	+++
	1.10.23	+++	++	-	-	-	-	-	-	-	-	-	+++	+++	+++
	1.15.23	+++	+	-	-	-	-	-	-	-	-	-	+++	+++	+++
Fasting	1.19.23	+++	+	+	-	-	-	-	-	-	-	-	+++	+++	+++
	1.31.23	++	+	+	-	-	-	-	-	-	-	-	+++	+++	+++



fasting animals gave the most variable results. It would, therefore, appear that the fasting guinea pig is to be preferred if the fresh serum is used within the hour.

On the other hand, when the guinea pig's serum has to be used after an interval of twenty-four hours, the superiority of the fasting animal is not at all evident. When kept in this way the serum of the animals which had been fed bread and milk one hour before bleeding proved to be less variable than did the serum of the fasting animals. The possible influence of feeding a more varied diet has not yet been studied.

In respect to the second question it appears that there is nothing gained by leaving the serum on the clot and that there is rather a tendency for the cytolytic power of the serum to deteri-

orate more rapidly in contact with its clot than when it has been promptly separated. Hemolytic tinting of the serum was also more marked after prolonged contact with the clot, interfering with the cytolytic power and making the titration more difficult to interpret.

The third question, that is whether the cytase should be used fresh or after an interval, is closely connected with the first; however, special points might be emphasized. Tables II and IV show that the poor results obtained with the serum of December 20, 1922, were not evident when the cytase was used within the hour.

Entirely irrespective of the tabulated findings a strong impression is left with the student that where the most delicate hemolytic titrations are desired, the preference would be in favor of the cytase from animals used within the hour. However, from the practical point of view, tests of cytase used within the hour do not precisely meet the requirements for the Wassermann tests; for the hemolytic titration alone consumes an hour, and the required fifteen or more hours' refrigeration of the unknown serum mixed with the antigen and the cytase, before adding the hemolysin and the sheep corpuscles, would, of necessity, make the cytase already several hours old when entering into combination with the corpuscles. Referring again to the frequency polygons, it is evident that kept cytase is more constant in action when the blood is taken from fed animals, and this superior keeping quality would counterbalance the advantage of the more delicate reaction of the fresh serum from fasting guinea pigs. For the actual Wassermann test, therefore, it would seem to be preferable to use the separated serum from guinea pigs fed on bread and milk, rather than from fasting animals.

Summary

1. The cytolytic activity of guinea pig serum is subject to wide variations, the causes of which are largely unknown.
2. Fasting guinea pigs yield a cytase more constant in activity when tested at once, but which readily deteriorates on keeping.

3. Fasting guinea pigs yield a cytase more constant in activity when fresh, but apparently inferior in keeping qualities to the serum of animals fed on bread and milk one hour before bleeding.

4. There is no advantage in leaving the serum on the clot.

5. It is best to break the clot at once after its formation and to centrifugalize at once, separating the serum and storing it in a separate tube immersed in ice water. In this way a larger yield of potent serum will be obtained.

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Discussion:

DR. MACNEAL: I am sure that the Wassermann test is of sufficient importance so that everyone is interested in every point that may affect our

technical procedure in carrying it out. The attempts to standardize the Wassermann test, or to set up any definite procedure which must be followed, will, of course, be combatted by those who think that the perfect Wassermann technic has not yet been attained. I feel that there is much to learn and I am sure that there are many here who have ideas about complement, which is one of the most delicate constituents entering into this reaction.

DR. PLAUT: In connection with the titer of the serum, I remember that I had great difficulty with the complement at times, especially in the spring and in the fall, when the food of the guinea pigs had to be changed, and we had such a decrease in the titer that we had to use very large amounts of complement, and this corresponds to some of those unknown factors which are influencing the titer of the complement. It may be due to some unknown things in the food, which would correspond to the differences here reported between the fasting and the fed animals. I would like to ask what practical advice would be given as to what we should do with the guinea pigs before taking blood for the Wassermann. I understand this will depend upon whether you are keeping the blood for a long time in the ice box, or whether you are going to read the test more quickly. It will be difficult to compare the tests by the two methods, with the readings done in one case after a short time, and in the other case, the next morning. Would it be possible to use different complement for both? This would add another difficulty for the comparison of the two methods.

MISS BAYLIS: For the Wassermann it would be preferable to use serum from the fed animals, separated, and kept in separate containers. If they are fed bread and milk an hour before bleeding they give the most constant results. Does that answer the question asked?

DR. PLAUT: It answers it in part. If I understood right, I think I heard that the serum of a fasting animal for the first hour after the blood has been taken is more constant than that of a fed animal, and only after some time has passed the serum of fed animals is better than the serum of animals which are fasting. Is there not then a difference if the readings are made after several hours, or if the Wassermann be kept on ice? I should think that by keeping the Wassermann in the ice box for a time the complement of fasting animals would be better, because it would be more constant.

MISS BAYLIS: No, the cytase of the fasting animal when separated and used within the hour gives the most delicate result, but according to the tables, the cytase from the fasting animal deteriorates more frequently, and, as the Wassermann requires a certain number of hours' refrigeration, it would be better to use cytase from the fed animals, which gives the most constant results when kept for twenty-four hours. We get a better result with the cytase of the fed animals if it is separated immediately after the blood is drawn and kept in a separate container.

A SIMPLE ELECTRICAL METHOD FOR THE PREPARATION OF COLLOIDAL GOLD

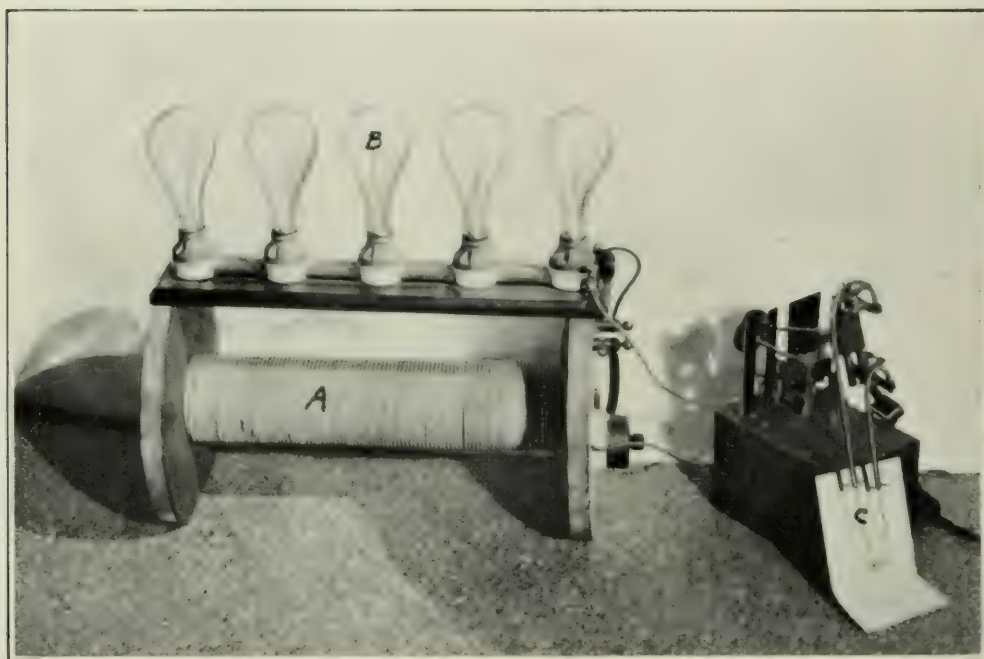
ADOLPH BERNHARD, B.S.

(From the Laboratory of the Lenox Hill Hospital, New York)

The method and apparatus described in this paper are not entirely original, since Beans and Eastlock¹ have described a similar procedure.

The electrically prepared gold keeps indefinitely, and has many advantages over the chemical method using reduction by formaldehyde. The specially cleaned glassware, triply distilled water, and the formaldehyde titrations are dispensed with in the new procedure.

The apparatus (Fig. 1) consists of a coil of five hundred feet number eighteen gauge asbestos covered wire (*A*), wound on an iron pipe one inch in diameter and one eighth of an inch thick. Five one hundred watt lamps (*B*) connected in parallel



are used as resistance. One wire leads from the source of the current supply through the lamps into the coil; the other end of the coil is connected to one of the gold electrodes (*C*). These electrodes are four inches in length, of number eighteen gauge, twenty-two carat gold wire. The second electrode is connected to the other pole of the current source.

Preparation of the Solution: Two hundred c.c. of hydrochloric acid solution having a pH 5.0 (N/100,000) are made roughly by adding two drops of normal hydrochloric acid to two hundred c.c. of distilled water. A clean pyrex beaker may be used to best advantage. The electrodes are immersed in this solution, and steady sparking is allowed to take place for two and one half minutes.

Stir the solution well and allow to stand overnight; decant, and it is ready for use.

It should be a magenta color and clear. To test the solution add 1.7 c.c. of 1 per cent. sodium chloride to 5 c.c. of the solution; almost complete reduction takes place within one hour, while reduction is complete within twenty-four hours. The results obtained with the solution prepared by the electrical method compare favorably with those obtained by the use of chemically prepared gold.

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Discussion:

DR. MACNEAL: I am sure that anyone who has used colloidal gold will be interested in this work. I should like to ask if you get hard and soft solutions, and queer-acting ones.

MR. BERNHARD: We have not experienced any of these difficulties as yet.

DR. ROHDENBURG: What has interested me is that we have not obtained any protected colloidal gold which so often happens with the solution made by the chemical reduction with formaldehyde. It has invariably reduced with sodium chloride. In spite of careful checking of the formaldehyde, every once in a while we struck a day when we had to make six or seven batches before we got a liter that worked, whereas now it is common practice to wait until the last minute and then tell the chemist to make up some more. Previously we always "played safe" by giving him two or three days' warning.

DR. CORNWALL: I would like to ask if the pH of all solutions prepared in this manner is the same? Does the length of time that the current is allowed to act effect the reaction of the solution to the spinal fluid? The method appears to have solved the difficulties encountered in the preparation of this reagent.

MR. BERNHARD: Regarding the question of protection, there is no other protective colloid present. We are simply taking a solution of a definite pH and dispersing gold particles in the suspension, and there is no reason why in the absence of any other colloid it should not remain the same.

As far as the pH is concerned, I have tried out different pH's. I started first with water. As you all know, with distilled water, the hydrogen ion concentration varies considerably. One of the things which I tried also was various buffers. They did not work, because they produced black solutions which were discarded. Gold solutions utilizing very dilute hydrochloric acid, such as this is, N/100,000, are very stable. We have done quite a number of spinal fluids using this gold, and we have not found as yet any of the off colors one gets with the other methods. This gold will not reduce itself. The other colloidal golds will reduce themselves and give a bluish-red color. We have not had this trouble.

DR. MACNEAL: Do you have to use especially cleaned glassware?

MR. BERNHARD: No, we use ordinary precautions in cleaning glassware. There is a sediment in this gold. If you pour off the supernatant liquid after standing it will not deposit any more. The tubes used in the test ought to be washed first with aqua regia, but we have a separate set of tubes and pipettes which we use only for colloidal gold.

A NEW METHOD OF DETERMINING GASTRIC ACIDITY *IN VIVO*

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In the following report, an electrical device to measure the total acidity of the gastric contents *in vivo* will be presented. The apparatus consists of two parts, a special stomach tube and an ohmmeter. The tube consists of two small platinum electrodes, which are mounted inside of a hard rubber, hollow, olive-shaped tip. This tip is connected to the end of two small rubber tubes, one tube being inside of the other. The inner tube is used to draw up specimens of gastric juice. Between the

two tubes are the wires which are connected to the electrodes.

The ohmmeter is an instrument which embodies the principles of the Wheatstone bridge. The arrangement of the various parts is shown in the diagram. The designations on the diagram can also be referred to the illustration.

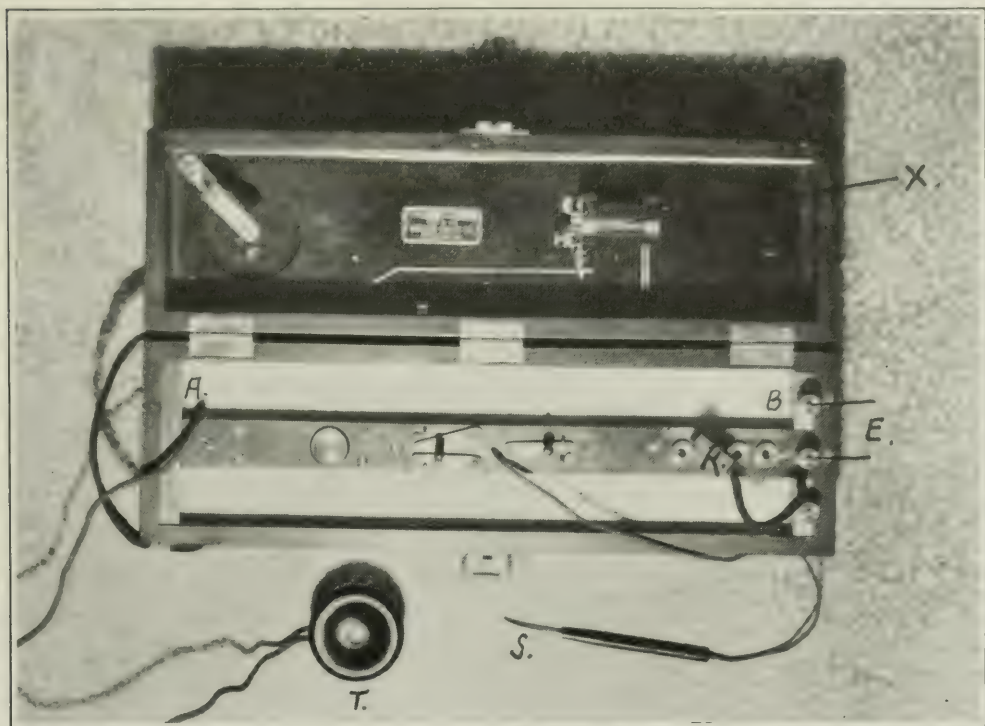


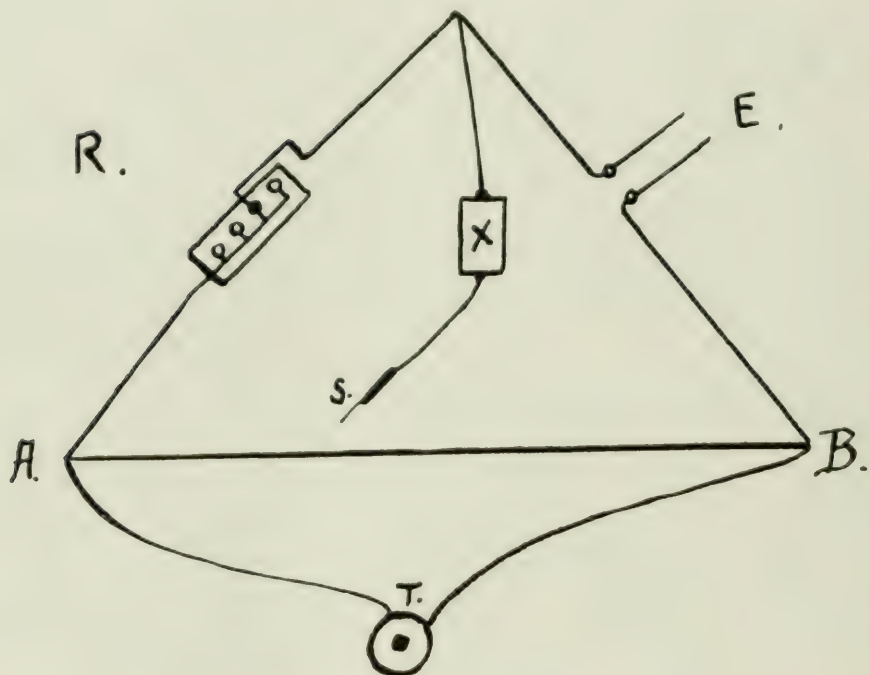
FIG. 1

AB is a platinum wire stretched across a graduated scale. *T* is a telephone receiver which is connected to each end of the wire. *R* is a known resistance in ohms. At *E* the two electrodes with an unknown resistance are placed. *X* is an induction coil which sets up an alternating current. *S* is a platinum-tipped stylet which is moved over the platinum wire, thus making contact.

In working this instrument the induction coil is first started. The buzzing of this coil can be heard in the telephone receiver as soon as the platinum wire is touched by the stylet. If now the resistance at *R* is equal to the resistance at *E*, there is a great diminution in the intensity of the buzz as the stylet in being run

over the platinum wire reaches the center of the wire. In other words R being equal to E , a balance is reached which must be in the center of the wire. $AS = SB$. If the resistance at E is

Diagram of Connections.



twice as great as our known resistance, the point of diminished sound on the wire will be one third of the way from A . That is $SB = 2AS$. The formula for all readings can therefore be expressed as:

$$R : E = AS : SB.$$

In the ohmmeter, however, the scale along the platinum wire is graduated to read off directly in ohms so that no calculating need be done.

The scientific principle which is made use of is that the strength of the solution can be measured by its facility to conduct electricity. It is known that various solutions differ in their ability to conduct electricity. The ability when equimolecular solutions are used, and placed under similar conditions, depends on

the degree of ionization, on the speed with which the ions move, and on the valence of the ions. The most highly dissociated acids are the best conductors, since they give large numbers of the speedy hydrogen ion. Hydrochloric acid is an example.

The highly ionized bases such as potassium or sodium hydroxid come next, possessing relatively speedy hydroxidions. The best conductors among the salts fall considerably behind both acids and bases.

Dilution has a great effect on the conductivity of any particular solution. That is, concentrated solutions conduct badly, but as soon as water is added, the ionization of the particular substance in solution is favored and in this way the conductivity is increased. Conductivity depends on the ionization because the ions are the carriers of the electrical charges.

To give these facts chemical significance, and for comparative purposes, the conductivity of various dilutions of dissolved substances is measured in a cell whose walls are of indefinite size and one centimeter apart. Ordinarily the resistance which a substance offers to the passage of an electric current is measured, and the conductivity is the reciprocal of this value.

When a cell is used, having electrodes of a definite size, the resistance becomes greater the more water is added. This statement may seem to contradict the one made above, namely that the more a solution is diluted the better its conductivity. In the first instance, however, we are dealing with a cell having walls of indefinite size and in the second case the walls of the cell have a definite size.

In order to be able to measure acidity by means of ohms resistance, it was necessary to construct a curve. Various dilutions of hydrochloric acid in water were made. The resistances in ohms of these dilutions were determined, and then titrated with decinormal sodium hydroxid. All the readings were made with the solutions at body temperature. From a curve that was made with the titrations of decinormal sodium hydroxid as abscissa and the resistances in ohms as ordinate it will be seen that as we approach very dilute solutions, the curve swings upward very rapidly, and that the dilutions at which the gastric juice exists can be read very accurately.

The tube is introduced into the stomach. It can be swallowed without any difficulty or discomfort because the tubing is small, and the tip is less than a centimeter in diameter. The patient is given two cups of thin oatmeal gruel to drink. The electrodes being in contact with this gruel, an electric current is started in the induction coil which is transmitted to the electrodes by means of the wires enclosed in the stomach tube. As the current goes through the gruel from one electrode to the other it is helped in its passage by the number of ions present. The number of ions in turn depends on the amount of acid present. Readings are made every five minutes, and about every fifteen minutes a specimen of gastric juice is drawn up through the central tube for titration, so that the two methods can be compared. The following cases show how closely the results obtained by the two methods agree.

Case No. I

Time after Meal	In c.c. of NaOH N 10 Electrical Determination	Chemical NaOH N 10 Titration
5 minutes.....	7½	
10.....	7	8
15.....	13	
20.....	14	
25.....	14	16
30.....	18	
35.....	23	
40.....	32	32
45.....	38	
50.....	44	
55.....	53	50

Case No. II

5 minutes.....	7	
10.....	7	
15.....	8½	10
20.....	9½	
25.....	11	
30.....	15	
35.....	21	
40.....	28	28
45.....	28	
50.....	31	
55.....	31	
60.....	33	34

Case No. III

Time after Meal	In c.c. of NaOH N ¹ / ₁₀ Electrical Determination	Chemical Titration
5 minutes.....		
10.....	4	
15.....	4	
20.....		
25.....	21	18
30.....		
35.....	23	
40.....		
45.....	30	34
50.....	35	
55.....	37	
60.....		
65.....	37	36

Case No. IV

5 minutes.....	3	
10.....	5	
15.....	7	
20.....	18	20
25.....	19	
30.....	23	
35.....	33	31
40.....	35	
45.....	39	
50.....	39	40
55.....		
60.....		
65.....	31	40

Case No. V

Time after Meal	In c.c. of NaOH N ¹ / ₁₀ Electrical Determination	Chemical Titration
5 minutes.....	3	
10.....	5	
15.....	6	
20.....	8	
25.....	8½	8
30.....	10	
35.....	11	10
40.....	14	
45.....	20	18
50.....	18	
55.....	20	

Ohms	Acidity	Ohms	Acidity
625	1	40	20
342	2	32.0	25
235	3	26.2	30
178	4	23.1	35
148	5	20.6	40
74	10	18.5	45
52	15	16.8	50

These are the ohms resistance obtained with varying degrees of acidity as measured by cubic centimeters of decinormal sodium hydroxid.

The same method can be applied to the intestine, but in this case it will be the hydroxid ion which conducts instead of the hydrogen ion.

Discussion:

DR. MACNEAL: I have the impression that we have been listening to a very important contribution to the study of gastric disease.

DR. ROHDENBURG: I have been much interested in the work that Dr. Maue has done. I do not think he has made it quite clear how the apparatus works. The tube is passed into the stomach and the electrical connection is established. This starts a buzzer going, and as the stylet is passed along the wire of the Wheatstone bridge, it reaches the point where the buzzing stops. This shows that the point has been reached where the standard cell current balances the current between the two tips of the electrode. The scale which is on the machine may readily be altered to read in c.c. of decinormal acid or alkali instead of ohms. The method renders it possible to measure the alkalinity of the intestinal juice, a matter not hitherto possible. Whether it will throw any more light on the physiology of acid secretion in the stomach than is possible by the Rehfuess meal is a matter for further investigation.

MR. BERNHARD: I know that Dr. Maue has tried his method with pure acid solution and water, and I wanted to know whether bread particles and protein would affect the conductivity.

DR. MAUE: Particles of bread going into the tube would interfere. That is why I have been giving the patients oatmeal gruel. To prevent the bread from going into the tube I am working on a new tip in which there will be only one opening at the end. This opening will be screened and I will be able to pull the juice directly into the tube and the bread will stay outside.

DR. LICHTENSTEIN: Can the organic acids be indicated, for example, lactic acid?

DR. MAUE: That depends on the ionization. Lactic acid is not highly ionized as compared with hydrochloric acid. At present I am only able to read the hydrochloric acid in the stomach.

DR. MACNEAL: These last two papers illustrate the breadth of scope of this Society, which is interested in the study of disease, not alone by the methods of pathological anatomy, but by all possible means.

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ACUTE PANCREATITIS WITH EROSION OF THE SPLENIC ARTERY AND FATAL HEMORRHAGE (Abstract)*

G. L. MOENCH, M.D.

From January 1, 1918 to August 31, 1923 the Office of the Chief Medical Examiner of the City of New York handled

* Presented October 10, 1923; published in full in *Jour. Am. Med. Assn.*, 1924, lxxxii, 360.

64,322 cases. Among this number there were roughly 28,000 deaths from violence and a little over 700 following abortions. About 9,500 autopsies were done.

Among all these deaths only twenty-one, including the case reported here, were due to acute pancreatitis. All of the cases, with the exception of one where the diagnosis was made from the symptoms alone, were corroborated by autopsy.

The etiology was generally indefinite; the symptoms on the whole were those described as typical except that the deep cyanosis often reported was not present as far as our records show.

The case presented here tonight is that of a woman forty years of age (C. S., Brooklyn, 1923, No. 2175) who died in shock two hours after admission to the Brownsville and East New York Hospital with all the symptoms of internal hemorrhage. The clinical diagnosis was ruptured ectopic cyst or ruptured ovarian cyst with hemorrhage.

The patient had been well up to the morning of the day of admission when she was suddenly seized with severe cramps in the lower abdomen and quickly went into collapse.

The autopsy showed an extreme hemoperitoneum; a necrotic, slightly bile-stained area in the pancreas, and erosion and rupture of the splenic artery. Uterine fibromyomata were also present. Gall stones were not found. The cause of death undoubtedly was the erosion of the splenic artery due to the necrosis of the pancreas. The cause of the pancreatitis, however, can only be guessed at. Because of the bile stain present an interference with the biliary flow may reasonably be assumed, even if no gall stones were found.

This case is unusual in that no symptoms referable to the upper abdomen were ever present, and because it is the only case of death from rupture of the splenic artery in our whole series of over 64,000 cases.

HEMATOCOLPOS IN A CHILD OF SIX WEEKS

(Abstract)*

G. L. MOENCH, M.D.

The case presented here tonight is that of a child who was found dead in bed by its mother.

* Presented October 10, 1923; will be published in full in *Am. Jour. Gynec. and Obst.*, 1924.

An autopsy showed no signs of violence; the lesions found were congenital atelectasis of the lungs; pulmonary edema; patent foramen ovale; a hemorrhagic cyst of the right ovary; erosion of the cervix; an imperforate hymen, and a hematocolpos the size of a golf ball filled with old tarry blood.

In interpreting the case I believe we must think principally of precocious menstruation, as there was no indication of past or previous inflammation (except the imperforate hymen) and absolutely no evidence of a hemorrhagic diathesis or allied condition.

Discussion:

DR. PLAUT: I should like to ask if there was any hemorrhage in the intestinal mucous membrane in the case of acute pancreatitis.

DR. MOENCH: No, there was no hemorrhage anywhere else in the body.

DR. PLAUT: There are the cases of hemorrhagic diathesis, so-called Winckel's disease, where the hemorrhages are in the intestinal mucous membrane. It is not absolutely impossible that this is one of those cases, with peculiar localization of the hemorrhages in the organs of the pelvis.

DR. MOENCH: The first case is the only one of its kind we happen to have, but I know of a second case of rupture of the splenic artery which Dr. St. George had at Bellevue Hospital, which was of traumatic origin. The patient had been kicked in the abdomen by a horse, and died of rupture of the splenic artery.

In regard to the second case, I do not believe that it belongs to the group of hemorrhagic diathesis, because usually jaundice, fatty degeneration, or at least marked petechiæ are present somewhere in such cases, and there was nothing of the sort here. Furthermore, the hemorrhage was not recent, so that I do not believe it was a contributory cause of death.

INSULIN AND BLOOD PRESSURE

PAUL KLEMPERER, M.D.*

(From the Department of Pathology and Bacteriology, New York Post-Graduate Medical School and Hospital)

This paper is the result of clinical and experimental observations made during the summer in conjunction with Dr. R. Strisower at the First Medical Clinic in Vienna. There are several facts well known to every clinician which suggest a relation

* Presented October 10, 1923; this paper will be published in the *Wiener klinische Wochenschrift* jointly with Dr. R. Strisower.

between carbohydrate metabolism and arterial pressure. The frequent coincidental occurrences of diabetes and high blood pressure, and also of hyperglycemia in hypertension on one hand, the combination of hypoglycemia and hypotension in Addison's disease on the other hand, might be mentioned in this connection. These clinical observations are corroborated by the effect of adrenalin injection and experimental epinephrectomy, both on the blood sugar as well as on the blood pressure. These considerations have suggested to us to test whether insulin would not exert an influence on the blood pressure also. The first experiments already made with an Austrian preparation on two cases of essential hypertension without renal symptoms and one case of diabetes with high blood pressure resulted several times in a rather marked gradual decrease of the high arterial pressure. Since, however, the Austrian preparation was not tested according to the directions of the Toronto Committee and since it did not exert a definite influence upon the carbohydrate metabolism, we decided to use, in our further experiments, only the insulin manufactured under the control of the Toronto Committee. Unfortunately we had to face the disadvantage that the Austrian pharmacies charged \$10.00 for an ampoule containing 100 units of insulin so that our experiments were limited, due to this great expense. Our observations concern, at the present time, two cases of diabetes with high blood pressure, four cases of essential hypertension, two cases of diabetes without increased pressure, two juvenile individuals with normal blood pressure and three cases of chronic nephritis.

In addition to these clinical observations, we have studied the influence of insulin upon the blood pressure of normal animals in several experiments.

Summarizing the results of our clinical and experimental observations we may state: In cases of diabetes with increased blood pressure and in cases of essential hypertension without renal symptoms, the injection of 10 to 12 units of insulin causes a drop in the arterial pressure. This decrease is gradual and

very slow and reaches its lowest level at the end of about two hours. From this time on the pressure rises again and reaches its former height after several hours. The maximal decrease is stated in per cents. 20 to 39 and in absolute figures between 32 to 62 mm. mercury. In diabetics and persons with normal pressure and in patients with chronic nephritis, we observed after injection of the same amount of insulin a decrease in the pressure of 2 to 11 per cent. The absolute figures, however, were only 2 to 15 mm., changes which are, as every experienced observer will confirm, within physiological variation. This conception is corroborated by the fact that in animals the intravenous injection of even very large insulin doses does not produce a decrease in the carotic pressure. In spite of previous insulin injection intravenous adrenalin injection produces the characteristic rise in the blood pressure. This also occurred when insulin and adrenalin were given simultaneously. The same observations hold good for pituitrin and the combined action of pituitrin and adrenalin. It seems to be important to emphasize that in the rabbit insulin did not affect the blood pressure, although the blood sugar dropped from 0.12 to 0.024. References in literature on observations of the blood pressure in insulin treatment are not very numerous as yet. Reports similar to these are, as far as I could review, not recorded. Only in the description of the clinical syndrome hypoglycemia we found remarks on decrease of the blood pressure in one or two cases, whereas much more frequently the pressure kept its height. The experimental work of the Toronto authors does not mention pressure tests, yet Italian authors, Sammartino and Liotto, report on a slow drop in the arterial pressure in rabbits in the hypoglycemic stage. We want, however, to emphasize that in none of our cases did those symptoms occur which were considered by the Canadian writers as characteristic for the hypoglycemic stage. Therefore, we feel justified in believing that the decrease in the blood pressure observed in our cases is not identical with that observed by the Italian authors. There is another factor, however, which has

to be considered as a possible cause of the drop in the blood pressure occasioned after insulin injection. The experiments of Popielski have proven that injection of extracts of organs produces a drop in the blood pressure which is identical with the influence of pepton injection. It might be suggested, therefore, to conceive the insulin effect as the non-specific result of the injection of an organ (pancreas) extract. In response to this objection we want to call attention to the fact that injection of pepton and organ extracts results only in a very brief decrease of the blood pressure. In our experiments, however, the pressure was decreased for two hours. On the other hand, insulin did not act upon normal human individuals and animals in a manner similar to that of pepton injection. Therefore, we feel justified in assuming that the action of insulin on the blood pressure is not identical with the action of pepton. Besides the positive results of our experiments the negative effect of insulin on the high blood pressure in nephritis is of great interest. It corroborates the conception mostly favored by the modern writers and newly emphasized by Volhard, that the high blood pressure in nephritis and in essential hypertension is of different nature and origin. Another interesting fact is the absence of any effect of insulin on the normal blood pressure. In this respect insulin cannot be compared with other drugs which also decrease the blood pressure, for instance, papaverin. There is, however, another far-reaching difference in that, with other therapeutic agents, we are unable to produce such extensive decrease in the pressure as we did in our cases with insulin. Our conclusions, however, must be very cautious, because we are unable to explain the mechanism of the insulin effect. Furthermore, the small number of our experiments further prevents us from drawing far-reaching conclusions. Nevertheless the results of our experiments were so definite that I felt justified in submitting our observations as a preliminary report to the Society.

Discussion:

DR. NOGUCHI: I should like to know if you have made simultaneous blood sugar determinations, and noted the effect of insulin on the blood sugar.

DR. KLEMPERER: No, we have not done that yet. We thought that if the insulin acts on the blood sugar it might also act on the blood pressure. The next step will be to examine patients with high blood pressure and to divide them into two groups: patients with high blood sugar and high blood pressure, and those without high blood sugar, but with high pressure. We were so limited by expense in our experiments that our work was confined to special groups of cases, and we restricted ourselves to certain cases of hypertension without symptoms suggesting a nephritic origin of the high blood pressure and also to real nephritis cases. We discussed this work during the summer, and decided that we ought to examine the patients for the blood sugar, to see if we could group the cases into those in which insulin has an effect on the blood sugar, and the blood pressure, and those without effect.

DR. COHEN: I should like to ask whether cases which show pathological changes in the vascular system, not cases of real nephritis, but of general arteriosclerosis with high blood pressure, would be influenced by insulin.

DR. KLEMPERER: My answer is the same as to Dr. Noguchi's question: It is very hard to say. This touches one of the most interesting and most difficult questions related to hypertension. We would not expect to find results of insulin treatment in these cases in which a definite change in the arteries has been established. I do not like to give an explanation, but I will try to explain it as we have done to ourselves, with reservations. We followed in our explanation the ideas of Pal on blood pressure. He has the definite idea that high blood pressure is the result of two factors: one factor is the spasm and contraction of the blood vessels, and the other factor is the tonus of the blood vessels. The contractions of the blood vessels can be influenced by papaverin; the tonus of the blood vessels can not be influenced by papaverin. Papaverin and epinephrin have an antagonistic action. Since in our experiments insulin did not act in the same way as does papaverin (no antagonism to epinephrin), we explain the effect of insulin in some way as an effect on the tonus of the blood vessel. In certain cases in the beginning of hypertension the blood pressure is not increased, according to Pal's observation, but the blood vessels have a very hard consistency, without being sclerotic. In our experiments the blood vessels became very soft after the injection, so we thought that insulin might act on the tonus of the blood vessel. We tried to gain information on this difficult subject, but we could not find an explanation. It is impossible to produce in animals the same condition as high blood pressure in man, and so experimental data are very scarce. All that we could do experimentally was to get negative results. We did not experiment on cases such as Dr. Cohen suggests, that is, arteriosclerosis with high blood pressure.

RETROPERITONEAL MYXO-LIPOMA *

D. S. D. JESSUP, M.D.

Retroperitoneal tumors arising between the folds of the mesentery and consisting in large part of myxomatous tissue are variously described as myxomas, myxo-lipomas, or where there is a sarcomatous element present, as myxo-lipo-sarcoma. They are alike in their origin and clinical features and course. Their growth is usually rapid with a tendency to recurrence. They have at times formed metastases in the liver and other regions. In their gross appearance with well-defined capsule and the ease with which they can be removed they are more like multiple benign tumors and their effect on the patient is usually local from the mechanical pressure of an abdominal tumor.

Four years ago two cases of myxo-lipo-sarcoma were shown to this society by Dr. L. C. Knox, coming from the Pathological Service of St. Luke's Hospital.¹ In both cases retroperitoneal tumors were removed and recurred within a few months.

The specimen now presented is a recurrent growth removed two years after the primary operation. The case was on the service of Dr. L. R. Kaufman at the Fifth Avenue Hospital, to whom I am indebted for the following notes on the history and clinical course:

The patient, a tall, thin woman, aged fifty-eight years, was first seen on June 20, 1921, because of a tumor of the abdomen, which she first recognized six months before, at which time a doctor advised operation. Her family history shows that her mother died at twenty-seven of pneumonia; her father at the age of seventy-six of "old age"; she was the only child. Aside from measles and pertussis in childhood, she had never been ill. Menstruation began at the age of fifteen, was regular and without pain; the flow was rather profuse, lasting five days; menstruation ceased at the age of forty-seven following which for a time she suffered from flashes.

History of abdominal tumor: She first noticed a lump in the right lower abdomen in July, 1920, which at first was movable, slightly tender, but without pain; in six months it grew approximately to twice its original size, and became rather fixed.

At the time of the first examination, June 20, 1921, the tumor was approxi-

* Presented October 10, 1923.

mately the size of a sixth or seventh month pregnancy, extending from just below the umbilicus. It was protuberant, smooth in outline, tense, with here and there irregular nodular formations at the lateral and inferior margins. Rectal examination showed merely a tumor mass filling the upper vaginal vault continuous with the abdominal mass; it was rather fixed with apparently a rather small, normal cervix to which the mass was connected. In the absence of gastro-intestinal symptoms, and from physical examination, a tentative diagnosis of ovarian cyst was made, and the patient was sent to the Hahnemann Hospital and operated upon July 6, 1921.

Operative Findings: A median incision was made. The gall bladder was normal, and was filled with stones. The appendix, pancreas, stomach and intestines were apparently normal. A semi-solid, globular tumor, about nine inches in diameter, was found arising from the mesentery over the mid-dorsal spine. A smaller tumor about three inches in diameter above this in the mesentery was enucleated separately. The tumors were enucleated without difficulty with ligation of the tributary blood supply, through an incision of mesentery closed with two-inch catgut. The uterus was very small, with many small fibroids, and there was a small cyst of the left broad ligament. A supra-vaginal hysterectomy was performed.

Post-Operative Course: The patient made an uneventful recovery from the operation and remained free from symptoms until December, 1922, at which time she noticed a re-formation of a growth similar to the previous tumor. She refused to submit to further examination, and did not return until July 30, 1923.

At this time she complained of loss of appetite, slight nausea, and occasional pain in the right lower abdomen; examination showed enlargement of the lower abdomen suggestive of about an eight-month pregnancy, the enlargement being a little more prominent on either side of the median scar of the previous operation; the scar was firm. The swelling was somewhat nodular, globular, somewhat elastic, with firm masses here and there, and appeared to spring from the abdominal and pelvic region.

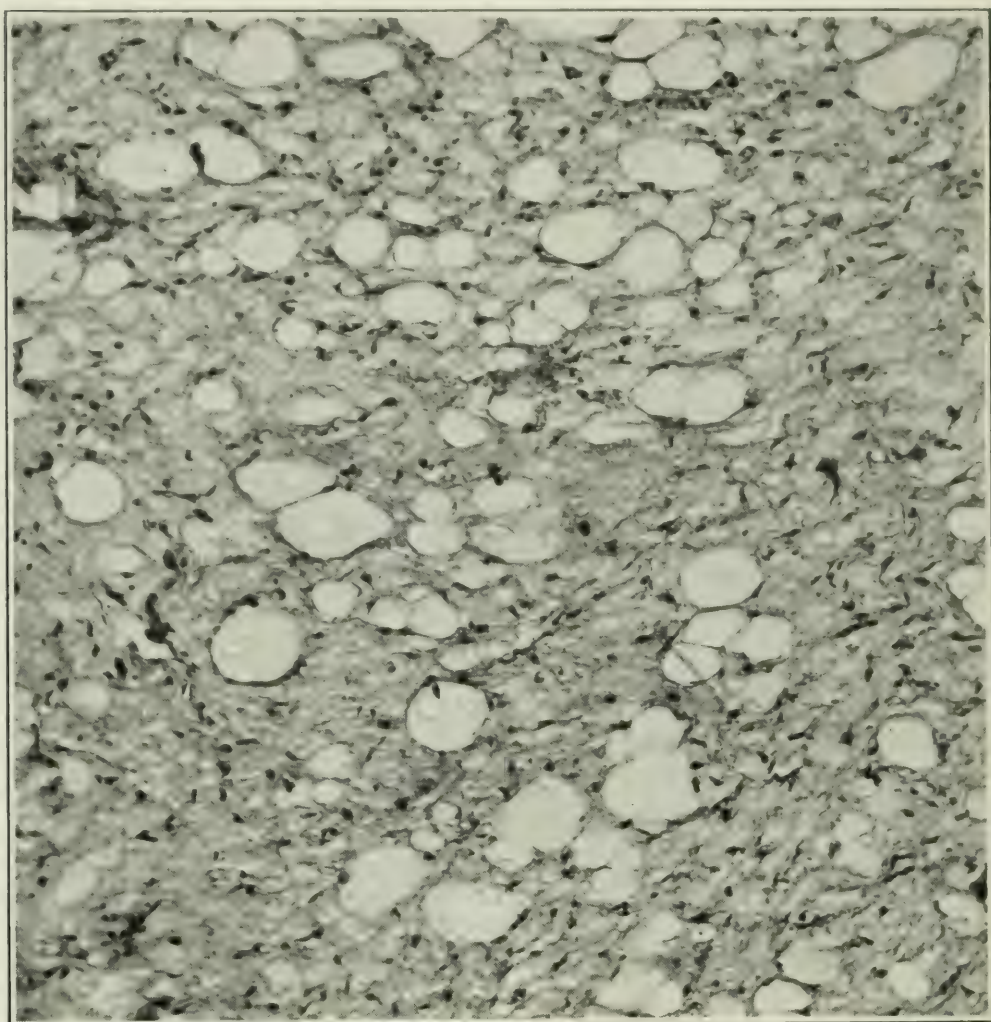
Rectal and vaginal examination showed the stump of the cervix to be freely movable, and the outline of the swelling was felt continuous with the abdominal tumor with a firm bridge across the anterior rectal wall.

Operative Findings: The patient entered the Fifth Avenue Hospital on August 2, 1923, for exploratory laparotomy. An irregular gelatinous tumor about nine inches in diameter was found, springing from the mesentery at the mid-dorsal line, freely movable, except for a few fine adhesions to the transverse colon. A second tumor, larger than the first, sprang from the mesentery about two inches above the origin of the former tumor.

Post-Operative Course: The convalescence in the hospital was somewhat disturbed by distention, which was readily relieved. The patient was discharged on August 22, 1923, in excellent general condition.

Pathological examination of tissue removed at the first operation showed in addition to the myomata of the uterus a globular mass measuring 20 x 15

cm., with a thin glistening capsule. On section this was composed of yellow gelatinous material with areas of hemorrhage, having the gross appearance of a myxoma. Microscopical examination of this showed a loose-meshed edematous-looking stroma with scattered fusiform or stellate cells mingled with fat-like spaces. There were also extravasations of blood.



F. A. H. Path. No. 8491. Retroperitoneal myxo-lipoma.

The tissue removed at the second operation (pathological number 8491) consisted of several globular masses of gelatinous-looking tissue with thin transparent capsule and somewhat lobulated outline. The largest mass was 25 cm. in diameter. On section the tissue was of a similar character throughout, very soft and gelatinous with areas of hemorrhage. Microscopical examination showed a picture identical to that seen in the first specimen, *viz.*, myxomatous tissue mixed with fat cell spaces with areas of hemorrhage. Examination of sections from many different portions failed to show changes that

could be called sarcoma, so that feature is apparently absent thus far in this case of retroperitoneal growth.

Note: Since the date of presentation of this specimen there has been a second recurrence described as follows:

November 6, 1923, the patient stated that aside from constipation requiring the use of cathartics, and at times slight pain in the right iliac region, she feels very well. She has gained one pound in weight in the last two months and, although she tires easily, she is able to go on with her work.

On examination a median scar extending from the umbilicus to the symphysis is firm and freely movable. Rectal examination is negative. The abdomen is distended; an irregular, firm mass about the size of a small orange 10 x 6 cm. in size is felt just outside the right edge of the rectus to the right of the midline with a lower edge about opposite the umbilicus. The mass extends upward from this point with irregular contour. It may be moved readily from side to side, but seems somewhat fixed at its posterior attachment; it is not tender and there is no pain referred at this point. The right kidney is felt normal; no other mass can be felt on deep palpation in the abdomen. Rectal examination is entirely negative. Glands throughout the body are not enlarged, and the general appearance of the patient suggests excellent health. There is a complete absence of cachexia.

Discussion:

DR. MOENCH: I would like to ask Dr. Jessup what he thinks the origin of the tumor was.

DR. JESSUP: Opinions differ as to how these myxomatous tumors arise. Ribbert believes that they are derived from embryonal connective tissue remnants, and in the retroperitoneal region this seems the most reasonable explanation.

THE VERNES FLOCCULATION TEST FOR SYPHILIS *

ADELAIDE B. BAYLIS, ADELE E. SHEPLAR, AND WARD J.
MACNEAL, NEW YORK

(From the Department of Pathology and Bacteriology, New York Post-Graduate Medical School and Hospital)

Laboratory tests upon the blood for the purpose of diagnosis and as a guide and control for the treatment of syphilis have become practically indispensable. Yet the exact nature of the peculiar substance or substances which are present in the blood during active syphilis and are thus tested for, still remains a mystery.

* Presented October 10, 1923.

The substance itself appears to possess a special affinity for lipoids and has been designated as the syphilitic reagin. The most popular test for this substance or group of substances is essentially that of Wassermann. In this test the serum of the patient is allowed to react with an antigen (an alcoholic extract of heart muscle) in the presence of the fresh serum of a guinea pig. The extent of the reaction between the lipoidophilic substance in the patient's blood and the lipoid antigen is measured by the effect which this reaction exerts upon the fresh serum of the guinea pig and this change in the serum of the guinea pig is, in turn, measured by the impairment of its subsequent dissolving effect upon sensitized red blood corpuscles. In the practical test this final solution of the red corpuscles may be influenced by many factors other than the concentration of the lipoidophilic reagin in the patient's serum. Those elements which tend to prevent the solution of the corpuscles are grouped under the head of anti-complementary substances, and those which tend to promote the solution are designated as native hemolysins and native complement of human blood. Most serologists heat the patient's serum before the test, so as to eliminate the action of native complement, and practically all serologists make special control tests for anti-complementary substances in the patient's serum. Various workers also attempt to control and to introduce corrections for variations in the native hemolysin of the patient's serum.

Perhaps the most serious source of variation in the Wassermann test is due to the somewhat uncertain quality of the fresh guinea-pig serum (cytase or complement). The activity of this substance varies in the blood of different animals and for the same animal at different times. Food of the animals and weather conditions appear to influence its potency within the animal body. After removal from the animal the activity of the serum is an extremely labile property, which is lost after a few days and appreciably diminished after forty-eight hours, even under the best storage conditions.

Jacobsthal¹ in 1911, showed that the reaction between antigen

and luetic serum is accompanied by the formation of a precipitate in the mixture, which he was able to observe under the dark-field microscope. The practical use of this observation had to be given up because quantitative estimation of the precipitate was difficult and even the qualitative readings were not sufficiently objective. Wassermann² evidently regarded these studies as of theoretical rather than practical value.

In the last few years there has been a renewed interest in the practical application of the precipitation or flocculation test to the diagnosis of syphilis. Meinicke,³ Sachs and Georgi⁴ and others in Germany, Dreyer and Ward⁵ in England, Kahn⁶ and Wile⁷ in this country have utilized the principle and have perfected the technic.

Arthur Vernes⁸ has for many years employed a system of laboratory control for the diagnosis and control of treatment based upon a flocculation test. His extensive work in this field has received only little attention outside of France. Cornwall and Aronson⁹ in 1920 presented in the *Journal of the American Medical Association* a brief review of the Vernes method as employed at that time. Since that time, however, Vernes has perfected his method so as to render the technic much more simple and the results highly objective. Various mechanical instruments for the exact control of the technical procedures have been devised to eliminate the variable human element. Most important of these is the photometric instrument of Vernes, Bricq and Yvon, by means of which it is possible to read, in an accurate quantitative manner, the opacity produced in a test mixture. The instrument is so designed that one may read directly on a printed scale the quantity of the precipitate in hundredths of milligrams per cubic centimeter.

It is not our purpose at this time to review the publications of Vernes upon this subject nor to describe the apparatus which he has devised. We expect to give a demonstration at the meeting of the Society for Experimental Biology and Medicine on October 17 at the New York Post-Graduate Medical School.

The object of this note is rather to call the attention of American workers to the new opportunities which the recent work of Vernes presents. During the summer of 1922, one of us (Baylis) had the opportunity to work for several weeks in Dr. Vernes' laboratory and after returning to New York suggested the importation of the equipment. The present note deals with the first hundred specimens examined here with this equipment.

Of the one hundred specimens, six gave negative Vernes readings; that is, the control tube of serum was slightly more clouded than the test serum to which antigen had been added. The readings are shown in Table I.

TABLE I

Specimens Giving Negative Vernes Figures (Flocculation Less than the Control)

Serum No.	Vernes Reading	Wassermann
23	— 0.07 mg.	—
20	— 0.04	—
49	— 0.03	—
65	— 0.03	—
107	— 0.02	—
38	— 0.01	not tested

In the series of one hundred specimens there were twenty-five which gave Vernes readings of zero and negative Wassermann. In all of these the translucence of the test tube could not be distinguished from that of the control by the Vernes photometer, reading in hundredth of a milligram per cubic centimeter. As these sera were all negative by the Wassermann test, their tabulation is superfluous. Their numbers in the series were 18, 19, 22, 27, 28, 36, 39, 43, 63, 66, 69, 70, 79, 80, 87, 89, 97, 99, 100, 102, 110, 115, 116, 121 and 124.

One specimen, No. 104, gave a Vernes reading of zero and a Wassermann reading of \pm with 0.02 c.c. and +++ with 0.05 c.c. of the serum, which is significant in diagnosis. Inquiry has therefore been made in regard to the clinical evidence in this case. The patient, F. R., male, aged 52, Dermatological Clinic

No. 17424, has leukoplakia of cheeks, tongue and palate, with granulating ulcer on the right half of the hard palate. He gives a history of syphilitic periostitis of right tibia five years ago. He was treated for syphilis and claims to have received one hundred injections. There has been no treatment for five years. He is married, without children. There have been two miscarriages. The clinical evidence would favor a positive diagnosis of syphilis in this case.

There were fifty-one specimens which gave Vernes readings above zero and below 0.10, figures which are not diagnostic of syphilis, according to Vernes, although, like the slight fixations in the Wassermann test, they may be significant in conjunction with other evidence. These specimens are listed in Table 2.

TABLE 2

Specimens Giving Vernes Figures Above Zero and Below 0.10 Mg.

Serum No.	Vernes Reading	Wassermann	Serum No.	Vernes Reading	Wassermann
32	0.09 mg.	—	105	0.04 mg.	—
90	0.09	—	33	0.03	—
84	0.08	—	45	0.03	—
94	0.07	—	57	0.03	—
111	0.07	++++	60	0.03	—
53	0.06	—	81	0.03	+++
92	0.06	—	16	0.02	—
109	0.06	—	17	0.02	—
123	0.06	—	50	0.02	—
15	0.05	—	54	0.02	—
29	0.05	—	59	0.02	—
78	0.05	—	67	0.02	—
83	0.05	++	75	0.02	—
93	0.05	—	106	0.02	—
103	0.05	—	117	0.02	—
2	0.04	—	118	0.02	—
3	0.04	—	25	0.01	—
5	0.04	+++	41	0.01	++
10	0.04	—	44	0.01	—
35	0.04	—	47	0.01	—
37	0.04	—	55	0.01	—
71	0.04	—	56	0.01	—
86	0.04	—	58	0.01	—
98	0.04	—	61	0.01	—
101	0.04	—	72	0.01	—
			119	0.01	—

The data in Table 2 indicate clearly that the Vernes readings and the Wassermann readings are not entirely parallel. Although both tests are designed to measure the reaction between a lipoid antigen and a lipoidophilic substance in the patient's serum, it would appear that other reactions and variations in the various reagents and possibly also small variations in technic, influence the results of the two tests differently. Of particular interest are the five specimens in this group giving a Wassermann test of positive diagnostic significance, two plus or above, namely, specimens 111, 83, 5, 81 and 41. The clinical evidence in respect to these has, therefore, been investigated.

Specimen 111 gave a Vernes reading of 0.07 mg. and a Wassermann reading of three plus with 0.02 c.c. and of four plus with 0.05 c.c. of the patient's serum. The patient, P. H., male, aged 43, Dermatological Clinic No. 18389, gives a history of gastric crises beginning eighteen months ago, with failing vision for ten years. Both blood and spinal fluid have given positive Wassermann tests. Argyll-Robertson pupils, slight ataxia in legs and positive Romberg are present. Spinal fluid shows increased globulin, 130 cells per cu. mm., and a colloidal gold curve 55542000000. This is obviously syphilis of the central nervous system.

Specimen 83 gave a Vernes reading of 0.05 mg. and a Wassermann reading negative with 0.02 c.c. and three plus with 0.05 c.c. of the patient's serum. The patient, H. D., male, aged 48, Dermatological Clinic No. 15946, gives a history of chancre twenty-five years ago. He complains of palpitation of the heart and his physician has made a diagnosis of aneurysm. He has been married twenty-two years. There have been six pregnancies. One child is living at age of seventeen years. The other pregnancies terminated in miscarriage twice, premature birth (7 months) once and four children (two pairs of twins) died within the first month after birth. This appears to be a case of syphilis.

Specimen 5 gave a Vernes reading of 0.04 mg. and a Was-

sermann reading of two plus with 0.02 c.c. and a reading of four plus with 0.05 c.c. of the patient's serum. The patient, S. F., female, aged 41, Dermatological Clinic No. 562, was married at age of twenty-one years. She has three living children. One died at age of three months of summer complaint. There have been two miscarriages, in the fourth and sixth pregnancies, both in the seventh month. She complains of daily headaches and pains in the right hypochondrium. Her blood gave four plus Wassermann reaction on June 4, 1919, and again on May 30, 1920. She received fairly regular anti-syphilitic treatment from June 4, 1919, to May 4, 1921. This is apparently syphilis but the diagnosis rests chiefly on the Wassermann test.

Specimen 81 gave a Vernes figure of 0.03 mg. and a Wassermann reading of two plus with 0.02 c.c. and a reading of four plus with 0.05 c.c. of the patient's serum. The patient, H. H., male, aged 23, Dermatological Clinic No. 18286, gives a history of chancre six years ago. He has given a positive Wassermann test previously and has been treated elsewhere. This is a recognized case of syphilis.

Specimen 41 gave a Vernes figure of 0.01 mg. and a Wassermann reading of two plus with 0.02 c.c. of the patient's serum and a reading of three plus with 0.05 c.c. of the patient's serum. The patient, H. S., female, aged 28, Dermatological Clinic No. 6121, has been married nine years. She has two children living, aged eight and six years, and has had two induced abortions. On May 24, 1921, she came to the Ear Clinic on account of deafness, which was diagnosed as due to syphilitic auditory neuritis. Her blood Wassermann was then four plus and she was transferred to the Dermatological Service for treatment. Treatment continued from June 14, 1921, to June 27, 1922. On January 28, 1922, and again on June 27, 1922, the blood Wassermann was negative. Treatment was discontinued on the latter date. Blood for the present test was taken on June 5, 1923. This is clearly a case of syphilis.

In all five of these instances the clinical evidence appears to favor the Wassermann result as against the Vernes reading.

In the series there were seventeen specimens giving Vernes readings of 0.10 mg. or above, regarded as of possible diagnostic significance (Table 3).

TABLE 3

Specimens Giving Vernes Figures of 0.10 Mg. or Above

Serum No.	Vernes Reading	Wassermann	Serum No.	Vernes Reading	Wassermann
74	1.24 mg.	++++	46	0.24 mg.	++++
73	0.90	++++	95	0.18	++++
88	0.67	++++	76	0.14	—
21	0.65	++++	48	0.12	+++
24	0.60	++++	51	0.11	+++
85	0.56	++++	30	0.11	—
82	0.46	++++	91	0.10	—
113	0.40	++++	4	0.10	+++
112	0.27	++++			

It will be noted at once that all the specimens giving Vernes readings of 0.18 mg. or above gave four plus Wassermann tests. One specimen, No. 74, gave 1.24 mg. flocculation by the Vernes method, approximately seven times that given by specimen No. 95 (0.18 mg.), although both were four plus by the Wassermann. One advantage of the Vernes test is that it gives at once definite figures for values beyond the range of the usual Wassermann readings and without additional labor.

Three specimens in this series, namely 76, 30 and 91, require special consideration because of the discord between the two serological tests.

Specimen 76 gave a Vernes figure of 0.14 mg. and a Wassermann reading negative with 0.02 c.c. and 0.05 c.c. of the patient's serum. The patient, J. F., male, aged 23, Medical Clinic No. 12334, is being treated for chronic bronchitis. The sputum is negative for tubercle bacilli. There is no history of syphilis.

Specimen 30 gave a Vernes reading of 0.11 mg. and a negative Wassermann test in both concentrations. The patient, J. P., aged 45, Medical Ward, Chart No. 31239, complains of abdominal distress and constipation. Examination shows jaundice,

edema of legs, tenderness over lower abdomen and a palpable tender mass in the abdomen. At exploratory laparotomy a diagnosis of generalized carcinoma of the abdominal viscera was made. No history of venereal disease could be obtained.

Specimen 91 gave a Vernes figure of 0.10 mg. and a negative Wassermann in both serum concentrations. The patient, G. C., aged 24, Nose and Throat Clinic No. 14924, complains of pain in swallowing and of loss of weight. Examination shows ulceration of epiglottis. The sputum contains acid-proof bacilli. There is no history of syphilis.

The clinical evidence obtained after the completion of the tests rather favors the Wassermann result in these three instances also. In fairness to the Vernes test it should be pointed out that Vernes does not consider a flocculation of 0.15 mg. or less as diagnostic unless on repetition the intensity of the reaction tends to ascend or descend. A constant flocculation of this low degree may occur in normal serum. Furthermore we, personally, lack experience as yet in application of the Vernes test, whereas the Wassermann test is being carried out by a technic in which we have long experience. In later tests, not included in the series here reported, we have met with instances of conflict between the Vernes reading and the Wassermann result, in which the clinical evidence favors the Vernes.

The methods for the serum diagnosis of syphilis are empirical and any estimate of their value must be based upon their application to a long series of cases. It would, therefore, appear quite unwise to advocate the substitution, for the Wassermann test with its abundant records, of any radically new procedure. The Vernes technic and apparatus, however, offer the possibility of eliminating altogether the variable red blood cells, hemolytic serum and the especially variable fresh guinea-pig serum from the test. It substitutes mechanical devices for the trained hand of the serologist and mechanical measurement for his trained eye, so that the whole procedure becomes highly objective. Finally it aims to measure, by the effect upon translucence of the fluid,

a single reaction between a specially prepared antigen and a substance in the patient's serum. In theory, the method possesses a strong appeal. In practice it appears to us, so far at least, to offer great promise. Already the results obtained by it have special value in measuring activity of syphilis above the range of a four-plus Wassermann reading. In patients giving doubtful or negative results by the Wassermann test, the Vernes reading is often helpful and we are inclined to give the latter great weight in the final judgment in respect to such specimens. Where there are grave discrepancies between the results obtained by the two methods we feel that considerable weight should be given to the Vernes figures, but until a much larger experience with it has been gained, we shall be inclined to rely more on the older test for diagnosis. As a guide to treatment the Vernes test offers especially splendid promise because of the more delicate changes which it records and especially the differentiation of specimens above the four plus and below the plus-minus of the Wassermann test. It is, therefore, our intention to use the Vernes test in conjunction with our Wassermann tests as a routine and we hope to be able, subsequently, to report a much larger series.

SUMMARY AND CONCLUSIONS

1. Of the one hundred specimens here reported, six were negative by the Wassermann test and gave Vernes readings below zero; twenty-five gave Vernes readings of zero and a negative Wassermann test; one gave a Vernes reading of zero and a slightly positive Wassermann test; fifty-one gave Vernes readings above zero and below 0.10 mg. and forty-six of these gave negative Wassermann tests. The other five gave significantly positive Wassermann tests and definite histories suggestive of syphilis. All five had been treated for this disease.

2. There were seventeen specimens which gave Vernes figures of 0.10 mg. or more, all but three of which were positive by the Wassermann test. These three gave relatively low Vernes figures, 0.14 mg., 0.11 mg. and 0.10 mg., and the clinical evidence in all three failed to suggest syphilis.

3. We are convinced that the mechanical mixer of Vernes and his accurately controlled technic for dilution of the antigen, on the one hand, and, on the other hand, his photometric instrument for the accurate measurement of flocculation, have brought new possibilities for accuracy in the reading of specific precipitation and that the use of these instruments places the precipitation or flocculation test on a new plane of objectivity and accuracy.

4. The flocculation test for syphilis, employing these instruments, promises to be a most valuable check upon the Wassermann test for diagnosis and especially as a guide in treatment. We feel, however, that we shall require a long experience with the method before the discarding of the Wassermann test can even be seriously considered.

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Discussion:

DR. NOGUCHI: I was very much interested in this paper. I think it is a good thing to have new methods tried out, and we may find more reliable ways of determining the reactions of the patients' serum. I remember Vernes' first paper, published during the war. I think he called his system "syphilimétrie." He used a colloidal suspension of an extract of dried heart muscle of the horse, employing mechanical devices to bring the lipoid into a uniform suspension. At that time he was measuring the reaction by a procedure similar to that of a modified Wassermann test, that is, by the degree of hemolysis produced by fresh hog's serum upon sheep corpuscles. I was rather doubtful of the Vernes method, since hog serum does not always contain the right proportion of complement and amboceptor, and without strict quantitative adjustment of the hemolytic system the reaction cannot give reliable results. From the report made

by Miss Baylis from Dr. MacNeal's laboratory, I understand that the work has since been further developed and that now Vernes omits the hemolytic system. I wish to ask whether the new flocculation test is easy to carry out, whether or not old serums, or serums containing hemoglobin, can be used, and whether the test can be applied to active as well as inactivated serum. Is there any precaution as to the quantities of serum or of colloidal suspension according as the serum has been inactivated or is used while active? Is it necessary that the glassware should be chemically clean, as is the case in carrying out Lange's colloidal gold test? I do not understand what you mean by measurement in milligrams, for if one lipoidal preparation is more susceptible to flocculation than another, surely a measurement of the flocculation by weight in milligrams can not hold except for a given reagent. Is it possible to prepare lipoidal reagents which are uniformly susceptible to flocculation?

DR. CORNWALL: I was very happy to hear this paper and to learn that other workers are trying the methods of Dr. Vernes. About three years ago, I began to work with the original Vernes reaction, employing the colorimetric scale, and it was a very difficult technique for one who did not possess the special apparatus employed by Dr. Vernes. It was necessary to improvise the equipment. The reason I undertook it was that after reading his preliminary publications it was obvious that Dr. Vernes had developed his method step by step after experiments based upon the fundamental principles of physical chemistry. I gave up the method when I learned that he was going to adopt a new technique and I should judge from the way Miss Baylis spoke that she is using his second method. He has a third one, and I have been working with that for several months. We are attempting to apply it only to controlled clinical cases, rather than to amass purely numerical statistics. In his second method the results are read numerically on an arbitrary scale and by means of a chart they are translated into terms of mg. of precipitate per c.c. of serum. With his third method the results are read directly by means of his photométer in terms of optic density. It is merely necessary to subtract the control reading from that of the reaction tube and the difference represents the amount of flocculation in terms of optic density. The Vernes reaction must be interpreted by a curve similar to the temperature. In other words, one negative reaction does not mean that the patient has not syphilis any more than one normal temperature in the course of a prolonged illness means that the case is afebrile. Vernes has certainly perfected a good method for the preparation of his antigen, adding the distilled water to the antigen or *vice versa* at a certain speed which must always be the same (1 c.c. per minute). He requires that the stirring be done always the same, *viz.*, 200 rotations per minute. His latest publications demonstrate the variations in the results that may occur when the method of preparing the colloidal suspension is altered. I should like to ask whether Miss Baylis used 20 or 25° for incubation. I have always used 25° C. for my work with his latest method, but originally used 20° C. It required a considerable amount of improvisation to do this without getting one of his water baths. I do not recall that I have had a single positive

Vernes in a case that was clinically non-syphilitic. I have had many single negative Vernes reactions in cases of old-treated syphilis with persistent 4 plus Wassermann reactions. I have had at least four or five cases of this type which we have followed with particular interest. They are cases of old vascular syphilis that have been treated for years and present only clinical evidences of cerebral vascular lesions. They have been treated more for the Wassermann reaction than for their symptoms. We have obtained negative Vernes reactions with several of these cases. Whether this means that the Vernes is more indicative of the clinical and pathological condition than the Wassermann, I do not know. I think that, in the final analysis, the comparison of the two reactions will have to be based on autopsy findings, and more especially on the examination for spirochetes, but the work of Dr. Vernes has great promise.

MISS BAYLIS: The use of the hog serum mentioned by Dr. Noguchi has been discarded together with the hemolytic system and the color scale of nine tubes.

The third and present method is a test for the degrees of flocculation, the interpretation being made with the aid of the photomètre, an instrument so adapted that it translates directly the amount of flocculation into mg. per c.c. of fluid and so delicately adjusted that it enables the operator to read in degrees of 0.01 mg.

Where there is a difference of less than 0.1 mg. of flocculation between the reaction and the control tubes Vernes does not give it a positive interpretation. In regard to the negative readings, Vernes teaches that in cases where clinical evidence would lead one to suspect syphilis the serum must give a negative reading for eight months, a test being made at least once each month.

As to the temperature of the liquids, under extreme weather conditions the test may be carried out at 25° C.; this I note is the temperature advised in the latest pamphlet of the Institut Prophylactique, but in Vernes' own laboratory the temperature used is between 18° and 20° C. for the suspensions and 25° C. for the incubation.

I hesitate to give any definite opinion regarding the use of old serums, feeling we are too young in experience. However, in the limited number of tests we have been able to do the age of the serum seems to make no difference.

DR. CORNWALL: I am quite sure that Vernes now uses 25° for the temperature of incubation. The regulation that Vernes laid down for a cure was that it should be negative for eight months. In his first report he called this the "Law of the Three Eights," eight being the number on his colorimetric scale indicating a negative reaction. The blood must be negative for eight consecutive months after the interdiction of all treatment and at the end of the eighth month the spinal fluid must be negative. That rather sounds like a dogmatic statement, but if one applies the same rule to the Wassermann it is not nearly so dogmatic as it seems. Dr. Vernes states that he has never seen a return to positive after the eighth month.

DR. MACNEAL: In regard to the difficulty of using the apparatus, it is

not difficult to use if one has an intelligent idea of it, and if everything goes well, you can run the specimens through rapidly; but the apparatus is not "fool-proof," and it is not wise to let someone unfamiliar with it work with it.

ANEURYSM OF THE ABDOMINAL AORTA WITH MES- ENTERIC THROMBOSIS *

JAMES R. LISA, M.D.

The patient, F. S., a white male thirty-six years of age, was admitted to the Metropolitan Hospital February 25, 1921. His chief complaint was shortness of breath. The family history was irrelevant. The personal history was negative except for chancre fourteen years previously. His present illness began three months ago with dyspnea and progressive loss of strength. For two days before admission the patient could not sleep because of severe epigastric pain, nausea and vomiting. On physical examination the chief findings were cyanosis, marked dyspnea, partial loss of vision, beginning optic atrophy, systolic murmur at the apex transmitted to the right, râles at the bases posteriorly, an ill-defined mass at the level of the umbilicus, marked sclerosis of the arteries, blood pressure systolic 240, diastolic 170, increased knee kicks, and bilateral clonus. The temperature was slightly below normal. Urinalysis was entirely negative. During the night the patient became delirious, breathing became Cheyne-Stokes in character and the temperature showed a slight rise. At this time the blood pressure readings were 210 and 180. Spinal puncture revealed a clear fluid under slightly increased pressure, globulin one plus and ten cells per c.mm. Three days after entrance retention of urine occurred. Catheterized specimen showed albumin, blood and pus. On the seventh day coma developed. There were two involuntary evacuations, the stools being tarry in character. After being in coma forty-eight hours, the patient died.

Autopsy findings: The autopsy was performed seventeen hours after death. The abdominal aorta presented a saccular aneurysm of the anterior wall involving the mouths of all the large branches—the celiac axis, the superior and inferior mesenteric and the renal arteries. The sac was filled by a large funnel-shaped laminated thrombus, the apex of the funnel leading into but not completely occluding the orifice of the superior mesenteric artery. The other arteries mentioned could not be probed from the aortic lumen. On opening these vessels, their mouths were completely occluded by the thrombus. That part of the aorta corresponding to the saccular dilatation showed numerous fine longitudinal striations and also numerous pearly plaques—the picture of syphilis—this area sharply demarcated from and in marked contrast to the rest of the aorta, which was grossly normal in appearance.

* Presented November 8, 1923.

The jejunum was dilated and felt like a rubber tube partly filled with water. In the portion opposite the mesenteric attachment were six flat circular purple areas, varying in size from two to six cm. The contents of the gut were fluid and bloody. No emboli could be demonstrated grossly in the small branches of the superior mesenteric vessels.

The other autopsy findings were prostatic abscess, acute ascending urinary infection, and lobular pneumonia.

Discussion:

DR. ROHDENBURG: It is interesting to compare the pathology of today with that of years ago. I have had an opportunity of going over all the old records of this Society, which, incidentally, will celebrate its eightieth birthday next year. Originally the Society met every two weeks through the year. For the first 174 meetings there was not a meeting at which an aneurysm was not presented. Now we see here but two or three aneurysms a year. Complications of the type shown in this case are frequently described in the old records of 1845 to 1849. It is rather remarkable that a lesion which was formerly as common as an aneurysm has become so relatively rare as it appears to be today.

DR. PLAUT: Concerning what Dr. Rohdenburg has just said, it is interesting to consider the changes of tissue affinity in syphilis. I think there is no other possibility in this case, and I think that Dr. Rohdenburg will agree with me that most of the aneurysms mentioned by him are syphilitic. The affinity of syphilitic infections seems to be changing. In making a study of the records of a large post-mortem service in Hamburg it could be seen that syphilis of the liver is becoming more and more rare, and syphilitic aortitis and neuro-syphilis are becoming more and more frequent. Why, I do not dare suggest. There are people that have the opinion that the different form of treatment may be responsible for the change. So it is not too difficult to believe that not only does the virulence of the disease change, but that the qualitative properties of the disease are changing too.

DR. LISA: In a very cursory examination of the literature I tried to find complications of aneurysm of the abdominal aorta similar to this case, and found one reference in which the termination was by mesenteric thrombosis in Trotter's monograph, "Embolism and Thrombosis of Mesenteric Vessels." I went over the literature rather rapidly back to 1910, and I could not find any recent reference to that complication. I failed to mention the Wassermann reaction in this case. The blood Wassermann was negative on two occasions, and the spinal fluid was negative in 2 c.c. amounts in water-bath fixation with plain and cholesterinized antigens. The last spinal fluid which was taken showed a weakly positive Wassermann, two plus with cholesterinized antigen, and one plus with plain antigen in 1 c.c. amounts. We were unable to do it in 2 c.c. amounts. In 0.5 c.c. amounts the reaction was entirely negative. I do not quite see how to explain the negative findings early in the case, in view of the reaction becoming weakly positive afterwards, except for the possibility of the man being under the influence of alcohol, because the history showed that he was a very heavy drinker.

DECIDUAL REACTION IN THE FALLOPIAN TUBE

ALFRED PLAUT, M.D.*

(From the Nathan and Miriam Barnert Memorial Hospital Association, Paterson, N. J.)

Decidual reaction in the Fallopian tube is a somewhat rare condition, and it is difficult to explain why it occurs in one case, and not in another. Perhaps, as someone has suggested, it would be better to ask why it does not occur in the majority of cases. When the ovum is implanted in the mucosa of the uterus, the endometrium reacts, but the fact that the decidual reaction of endometrium is to be found in every case of ectopic pregnancy shows that it is not the irritation by the ovum which causes the decidual reaction.

The case I wish to report is that of a woman twenty-five years old with the clinical signs of ectopic pregnancy. A typical specimen was removed at operation. It was a pearshaped tube which after hardening and cutting showed the usual picture of a huge blood clot without details. On microscopical examination I could not find any remnants of the embryo itself, and only after a long search some chorionic villi were found. They were in different degrees of necrosis and partly surrounded by leucocytes. In the ampulla of the tube, where the hemorrhage was located, the wall showed only uncharacteristic layers of fibrous tissue and muscle fibers, and a long search was again required to find a few mucosa folds. They were thin, compressed, but otherwise quite normal. However, near the middle of the tube on the point where the thickening made by the hemorrhage subsided, the stroma of the tubal mucosa showed the typical decidual reaction.

There is no question about the decidual reaction here; the lantern slide and microscopic examination show all the characteristics necessary for this diagnosis. Flattening of the epithelium in those parts of the folds where the reaction took place can be seen, and even where only a few of the stroma cells underwent the swelling, the epithelial cells covering them are flatter than their neighbors. The whole length of the folds is not changed in an equal degree; the basal parts are not changed, and the swelling of the cells is more marked near to the end of the fold. This seems to be the rule, as other authors report the same findings. However, the isthmus of the tube was perfectly normal, and in this case the rule found by others does not apply, that the decidual reaction in the tube is more marked as we go away from the point of implantation.

* Presented November 8, 1923.

The question arose if in this case the serosa of the peritoneum showed decidual reaction in a higher degree than usually, as found by Schmorl. Since the patient did well after the operation, only the appendix could be examined, and in its serosa no decidual reaction was to be seen.

A NEW ANATOMICAL FINDING IN THE APPENDIX

Under the slightly thickened serosa of the appendix gland ducts, surrounded by lymphatic tissue, were lying. Their resemblance with the glands in the mucosa of the appendix is almost complete in the form of the cells and of the nuclei, in their staining, in the surrounding lymphatic elements, and even the product of the secretion of these intestinal epithelial cells can be seen. I do not know if they are in connection with the mucosa, as I could not do serial sections. Nevertheless, I see no other possible explanation. I do not think that serosa cells which by some inflammatory process can assume gland-like formations can give a picture like this, and I cannot see how the surrounding lymphatic tissue can be explained by this. The appendix has been studied in such tremendous numbers that I was astonished not to find in the literature a report of a thing like this; it must be extremely rare.

Note: Since presenting this paper, I have had the opportunity to compare my slides with slides of endometrial serosa adenomyosis, which Dr. Sampson from Albany was kind enough to send me. The comparison confirms me in my first opinion that these gland ducts in the serosa of the appendix are not identical with Dr. Sampson's cases, but are intestinal glands.

Discussion:

DR. SCHLEUSSNER: I have seen one specimen recently of a definitely chronically inflamed appendix where the lumen took a little dart out into the mesentery and came back into the center of the appendix again, and that little tract was lined by real mucosa with glands and lymphoid tissue as in the section shown. That was in a really definitely inflamed appendix, while in Dr. Plaut's specimen there is no evidence of a chronic inflammatory process. But perhaps it might be that this represents a residuum of some previous inflammatory process.

DR. MOENCH: In regard to the decidual reaction in the tube, the tube usually does not show decidual reaction unless there is a pregnancy present. With menstruation I have never seen any definite decidual reaction in the tube, and this is due to the different anatomical structure of the endometrium and the mucosa of the Fallopian tube. However, in pregnancy, you may see decidua, although some authors do not regard any such change in the tube as true decidua equivalent to a uterine decidua. The only explanation for an ectopic decidua is that under the marked stimulation of the ovum actually present in the tube, decidual cells are formed. The stroma of the endometrium is regarded as of mesodermal origin, and as formed from connective tissue, and I suppose the connective tissue in the tube may also, if necessary, change itself into decidua.

In regard to the appendix, a number of cases have been reported where an adenomyositis has been found in both the large and small intestine. Furthermore, in the uterus and sometimes in the tube, one can find adenomyositic reactions in which, even on serial section, there is absolutely no evidence of the glandular growth being connected with the interior of the uterus. Robert Meyer, of Berlin, has described a number of cases where typical glands surrounded by characteristic cytogenic tissue were derived from the peritoneum itself. I have seen one case in the tube where typical glandular structures could be traced from the surface of the peritoneum into the musculature of the tube, and there was no diverticulum in the tube, nor was there any connection between the mucosa of the tube and the peritoneum. I should not be surprised if this appendix was one of those cases where there is an adenomyositic reaction, possibly due to embryonal displacement, possibly due to an inflammatory condition, derived from the peritoneum.

DR. SEECOF: I think that several men, particularly Sampson (*Arch. Surg.*, 1922, v, 217), have pointed out that many of these glandular elements found on the peritoneal surfaces originate from the endometrium and from the tubal mucous membrane. Some experimental work was done along these lines (*ibid.*, p. 281), and I believe this case might possibly be one of a peritoneal implantation from the uterine or tubal mucous membrane.

DR. EWING: It seems to me that Dr. Plaut's explanation is the only one which is reasonable. If you look at the sections you will see that they are absolutely identical with intestinal mucosa with the lymphoid stroma about them. I wonder whether this might not be of any significance in connection with some of the mucoid carcinomas which develop in the abdominal cavity without any connection with the intestinal wall.

DR. KLEMPERER: In cases of cystic colitis Loehlein explained the presence of glands in the muscular coat or even near the serous surface of the colon by the prolongations of glands. The same picture can be seen in a chronically inflamed gall bladder in which also epithelial structures are seen, sometimes near the serous surface. I would like to ask if there was any sign of chronic inflammation in the appendix. However, that would not explain these findings. In chronic dysentery these long prolongations of the mucous membrane near the serous surface are frequently found, whereas in chronic appendicitis such findings have not yet been reported.

DR. PLAUT: First let me remark that the diagnosis of ectopic pregnancy was very easy, because we did find chorionic villi. The explanation that the direct irritation of the ovum in the Fallopian tube may give origin to the decidual reaction cannot satisfy, since in most cases of tubal pregnancy we have no reaction, and then decidual reaction in the tube has been described in uterine pregnancy of man as well as of animals, especially the pig.

About the comparison with adenomyositic conditions, nothing resembling muscle elements could be found around the ducts. Ideas have changed in regard to adenomyomas which are situated not just in the uterus or the tube. For instance, those tumors of the umbilicus which have been spoken of as such are now spoken of as originating from the serous layer of the peritoneum. I saw one slide, and I must agree with the author that no muscle fibers are to be

found in those pictures which have a great resemblance to the findings here in the serosa of the appendix. The surrounding cells are typical, somewhat spindle-shaped cells, and not round lymphatic cells. The adenomyositic conditions spoken about are not in the intestinal wall, if I understand rightly; they are all in the Fallopian tube. I have had no experience with the cystic conditions which Dr. Klemperer mentioned.

THE THYROID FACTOR IN PANCREATIC DIABETES. AN EXPERIMENTAL STUDY *

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This paper is based upon experimental studies which were carried out at the Department of Clinical Pathology, College of Physicians and Surgeons, Columbia University, during the last three years. Eighty-five dogs were used for the experiments. As several papers pertaining to the subject have appeared from time to time, a brief survey of the work will be given.

Since some of the endocrine disorders are polyglandular and since the pancreatic hormone has been discovered, one is justified in speaking of an interrelation between the insular apparatus and the thyroid gland. It should be mentioned at the start that while the relation of the pancreas to the thyroid may be shown experimentally to exist, one is at a great disadvantage in discussing the relation of the thyroid to the insular apparatus inasmuch as toxic goiter or hyperthyroidism has never been produced in animals.

The reports on thyroid feeding in regard to the appearance of glycosuria are rather conflicting. While Magnus Levy¹ writes that sugar may appear in the urine of man as well as dogs from large doses of thyroid, Carlson² denies such effects of the drug in dogs.

From our own experiments we concluded that large doses of thyroid, when administered by the stomach tube, may produce even a persistent hyperglycemia, provided alcoholic extracts are

* Presented November 8, 1923.

prepared in a manner similar to those of insulin. Alcoholic extracts from fresh young calves' thyroid, as shown by one ² of us recently, as well as commercial thyroid preparations, lower the blood sugar in normal as well as in diabetic dogs. In one of our ¹ papers we fully discussed the relation of the thyroid to the pancreas on clinical grounds and the following points were brought out:

1. Spontaneous glycosuria occurs in hyperthyroid conditions.
2. The simultaneous occurrence of toxic goiter and diabetes mellitus is extremely rare.
3. Subthyroid persons may develop spontaneous glycosuria as well as diabetes.
4. Myxedematous individuals are not liable to become diabetic and their glucose tolerance is high.
5. A spontaneous cure from diabetes may occur through hypoplasia of the thyroid from causes as yet unknown.
6. Because of the hypoplastic type of thyroid in advanced years as evidenced by the flat epithelium, the course of diabetes is mild in elderly people.
7. Because of the hyperplastic type of thyroid in the very young as evidenced by columnar epithelium, the course of diabetes is severe in children.
8. Lowered glucose tolerance manifests itself in every case of hyperthyroidism whether fasting hyperglycemia is present or absent.

The behavior of the thyroid in diabetic patients was recently presented by Wilder and his co-workers. Throughout their experiments the glucose tolerance varied inversely with the metabolic level, rising as the rate fell, and falling as the rate rose. The glucose utilization was best when the rates were lowest and acidosis was either controlled or decreased; when the basal metabolic rates rose, sugar tolerance diminished and acidosis increased.

The fact that lowered glucose tolerance is common in all cases of hyperthyroidism tends to show that the insular apparatus in this condition is unbalanced, though actual pathological lesions

in the Langerhans islands may be absent. It seems then that an over-functioning thyroid always does some harm to the islets and therefore total integrity of the insular apparatus is a *sine qua non* for normal glucose tolerance. While in hyperthyroidism the insular apparatus is out of balance through the excessive secretion of thyroid hormone, lowered glucose tolerance is a constant finding in dogs after removal of small portions of pancreatic tissue. It is generally accepted that the remaining pancreatic tissue compensates for the removed tissue. This compensation, however, may be sufficient to prevent hyperglycemia, but insufficient to prevent lowered glucose tolerance.

1. The removal of the pancreatic tail alone leads to hyperglycemia several days after the operation. However, in exceptional cases the glycemia may be temporarily high or may even be normal throughout, but these dogs are nevertheless diabetic since their sugar tolerance is greatly diminished. In the remaining pancreatic portions the islands are decidedly increased in number. Although anatomical compensation established itself, physiological compensation is lacking. A lack of physiological compensation with evidence of anatomical compensation of the insular apparatus may be shown to exist in those cases of human diabetes in which the Langerhans islands were found to be hypertrophied. MacCallum,⁶ Cecil⁷ and many others have described such necropsy findings in the pancreas of diabetics.

2. In removing on a later date the duodenal portion in the same animal, or in removing the splenic and duodenal portions simultaneously in other dogs, the animals show persistent hyperglycemia. The increase in the Langerhans islands in the remaining middle portion is still marked. Although anatomical compensation manifests itself, physiological compensation is greatly diminished.

3. When after almost complete pancreatectomy a dog develops intense and persistent diabetes, an occasional island may be found in the remnants, or when many islets are present they do not have the normal appearance and remind one of degen-

erated renal glomeruli. Thus the compensatory mechanism of the remaining islands is about nil. There is obviously no compensation in an almost completely depancreatized dog.

4. A lack of physiological compensation may also be noted in dogs after ligation of one pancreatic duct. Such dogs remain persistently hyperglycemic, similar to those after partial pancreatectomy. Of course when both pancreatic ducts are ligated the blood sugar remains normal. An alcoholic extract of such a pancreas, as shown by Banting and Best, reduces the blood sugar in a diabetic dog and in a normal dog, and when the dosage for the animal is too large the so-called insulin shock manifests itself.

Since the removal of smaller pancreatic portions always leads to lowered glucose tolerance, the anatomical compensation in the remaining islands is not sufficient to uphold the equilibrium of the pancreatic hormone in the blood stream, especially in the tissues. The lack of insulin which occurs after removal of the pancreatic portions is in direct ratio to the amounts of tissue removed.

Experimental diabetes may be divided in three groups: *i.e.*, insular insufficiency of first, second and third order. Obviously hyperglycemic dogs after ligation of one duct belong to the second group.

Our chief object is to show that dogs in whom various grades of insular disorders are induced may become free from hyperglycemia and from glycosuria and show increased sugar tolerance after depriving them of the thyroid secretion, by complete or almost complete removal of the thyroid gland or by ligation of all thyroid arteries.

When the thyroid has been completely removed in diabetic dogs in one sitting, the animals succumb usually on the second or third day after the operation, even when tetany does not ensue. The operation, therefore, must be performed in two sittings: the removal is either preceded by partial ligation of the thyroid vessels, or one lobe is removed and the second lobe at a later

date. After such procedures the dogs may remain in good condition indefinitely. Such dogs are lively, gain in weight and show increased sugar tolerance. Of course when completely depancreatized, dogs are deprived of their thyroid secretions and they succumb although life is prolonged in comparison with dogs after complete pancreatectomy without removal of the thyroid.

The hyperglycemia persists when a larger fragment is left or when partial ligation of the vessels is done; when infection sets in or when the animals are seized by tetany. But when one succeeds in checking the tetanic attacks by calcium preparations, glycosuria disappears and the blood sugar becomes normal. We shall also make a comparison between the effects of insulin and the effects of thyroidectomy on the blood sugar curve. While after the use of iletin the result is transitory, after removal of the thyroid the effect is a permanent one. Furthermore, because of the increased sugar tolerance of the diabetic dogs after thyroidectomy, the iletin dose required to produce insulin shock is less than before the thyroid removal.

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Discussion:

DR. ROHDENBURG: I have followed the work of Dr. Friedman with much interest, and I think his results open several paths for speculation, if not for further research. I have observed two cases in human beings in which a very marked glycosuria with all the elements of diabetes, loss of weight, high blood sugar, and polyuria, cleared up after a thyroidectomy. Those cases have been reported elsewhere. Of particular interest are the results Dr. Friedman has shown in his dog with tetany. During the period in which the calcium in the blood is lowered, *i.e.*, tetany, sugar appeared in the urine. The investigations of Underhill and his co-workers show that the equilibrium of carbo-

hydrate metabolism bears a relationship to the calcium content of the blood, for by the injection of calcium salts, the glycemic reaction, which follows the injection of adrenalin or of glucose, can be markedly inhibited. An increase of magnesium in the blood markedly lowers the stability of the glucose metabolism.

DR. EWING: Among other things, I was especially interested in the demonstration that ligation of one portion of the pancreatic duct lowers the sugar tolerance. There are cases of diabetes in which the sole pathological condition in the pancreas consists in obstruction to the outflow of the pancreatic fluid, the dilatation of the ducts and acini, and hypertrophy of the islands.

DR. PLAUT: It would be very interesting to know how far the things which have been demonstrated here are due to a real specific action of the thyroid hormone, and how far they may be due to the differences in metabolism. In diabetes in man things raising the metabolism, for instance, eating meat with a high specific dynamic action, increase the output of sugar and increase the sugar in the blood. Removal of the thyroid gland lowers the metabolism. Certainly it lowered the metabolism of those dogs. It would be of great interest and of great advantage in this piece of research to know what percentage of the reaction is due to change in metabolism, and what is due to the real specific action of the thyroid contents.

DR. FRIEDMAN: As I understand Dr. Ewing, he said that obstruction of the pancreatic duct does not lead to any glycosuria.

DR. EWING: Yes, I have autopsies on cases of fatal diabetes in which the only change in the pancreas was an obstruction of the ducts, with dilatation of the acini and hypertrophy of the islands.

DR. FRIEDMAN: This may perhaps be due to the fact that where there is anatomical compensation there may be a lack of physiological compensation. I simply offer that as an explanation.

In regard to the remarks made by the last speaker, I would like to say that this work is not yet finished. We have certainly many things to take up, and the basal metabolism is among them. I only wanted to report that with thyroidectomy we can accomplish more in animals than by iletin injections, and we know that with iletin injections we must have the patients on a strict diet, while the dogs were not on a strict diet in our experiments.

NECROPSIES OF THE NEWBORN *

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Most of the literature on the necropsies of the newborn concerns itself mainly with the etiology and pathology of intracranial hemorrhages, and comparatively little has been reported on any other postmortem pathological findings. The notable ex-

* Presented December 13, 1923.

ception is the second paper by Warwick,¹ where she takes up in detail all the pathological findings in 200 necropsies, performed by different physicians. Our report will include all the macroscopical findings in forty-six autopsies performed on stillbirths and infants dying within the first week, and will not concern itself with the cause of death in these cases, for this phase has been reported elsewhere.² The microscopical studies of some of the pathological lesions, especially of the brain, are now being pursued and will be reported at a later date. The material was nearly evenly distributed between the two sexes: there were twenty-five male and twenty-one female infants.

TABLE I

	Per cent		Per cent
Full term..... 35	76 {	stillborn 15	32.6
		living 20	44.4
Premature 11	23.9 {	stillborn 6	13
		living 5	10

The total stillbirths were 21 or 45.6 per cent. and the total living 25 or 54.4 per cent. Definite macroscopical lesions were found in forty-two cases, while the four remaining cases were premature stillbirths without any demonstrable macroscopical lesions. A few cases showed only edema of the brain or congestion of cortical vessels. These specimens are being studied microscopically, for Schwartz³ has demonstrated, in cases with supposedly negative autopsy findings, scattered intracranial hemorrhages.

Intracranial Lesions.—Intracranial macroscopical lesions were present in thirty-three cases, eighteen showing hemorrhages and fifteen congestion or edema.

TABLE II

Intracranial hemorrhage: 18 or 40 per cent.

Stillbirths 5	{	Full term 5
		Premature 0
Viable 13	{	Full term 11
		Premature 2

This was associated with hemorrhage in other parts of the body 7 times or 39 per cent. In the eighteen cases with macroscopical intracranial hemorrhage only five were stillborn while thirteen lived from a few hours to five days, and of these only two were premature, showing, as has been found by other investigators, that not only in premature but even in full term infants intracranial hemorrhage is very frequent. Most of these hemorrhages were subdural and covered part or the whole of the cortex, and at times were located between the two lobes of the cerebrum. The basal hemorrhages usually surrounded the medulla and cerebellum and in a few cases extended into the cervical canal without any other demonstrable lesion in this location.

Of the eight tentorial tears found six were accompanied by basal hemorrhages, and in these the inferior layer was torn. The right tentorium was torn six times and the left twice.

Three (lateral) ventricular hemorrhages were found; two were associated with hemorrhage in other parts of the brain, while in the third (a premature birth) it was the only lesion found. In one case hemorrhage in the pia was the only intracranial lesion found.

A large intracerebral hematoma, displacing a large part of the cerebral tissue of the right lobe posteriorly, was found in one case. This was not a birth injury, but was due to some therapeutic measure, and the puncture-opening in the longitudinal sinus where the needle emerged and entered the cerebrum was demonstrated.

TABLE III

Intracranial congestion and edema; 15 or 32.6 per cent.

Stillbirths5	{ Full term3
		{ Premature2
Viable10	{ Full term8
		{ Premature2

Congestion and edema were the only lesions in four cases, while the other eleven cases showing these intracranial lesions were associated with pathological lesions in other parts of the body.

Cranial Bones.—Five cases, all full-term stillbirths, presented injuries of the cranial bones; they were either dislocated, crushed, or fractured, and four of these were associated with intracranial hemorrhages.

Cephalohematoma was present in sixteen cases. Five were associated with intracranial congestion or edema and eleven with intracranial hemorrhage; therefore, every case of cephalohematoma was associated with some intracranial lesion. In two cases the cephalohematoma was traced as originating from a fractured cranial bone with an intracranial subperiosteal hemorrhage. This is of great prognostic importance.⁴

Thirteen skulls showed overriding or widely open sutures extending from root of nose to occiput, and only three of these were premature births, showing that the failure of ossification is quite frequent in full-term infants. Intracranial hemorrhage was present in five, strongly suggesting a possible etiological factor.⁴

Spinal Cord and Column Lesions.—Out of four cases with definite pathological lesions of the spinal cord three showed subdural hemorrhages of the cervical region and one a myelomeningocele in the sacral area, associated with a purulent basilar meningitis. One of the three cases showing hemorrhages was a breech extraction and presented a dislocation of the first and second cervical vertebræ with a tear of the ligaments and a subdural hemorrhage in the meninges of the entire cervical cord. The other two cases were associated with intracranial hemorrhages of the basilar type.

TABLE IV

<i>Atelectasis</i>	<i>Intracranial Complications</i>
Full term26	Hemorrhage10
Premature9	Cortical congestion8
Complete28 (stillborn 19)	Negative17
Partial7	

Intrathoracic Findings.—Atelectasis of the lung is the most frequent finding in the chest; thirty-five cases showed this condi-

tion, either partial (7) or complete (28). Partial atelectasis was found to involve a whole lobe, or parts of a lobe on one or both sides. Two cases showed areas of hemorrhage in the lung parenchyma and were associated with hemorrhage in other organs. Of the seven cases of partial atelectasis only two were associated with intracranial hemorrhage, therefore, this is not as frequent an association as other observers find it. Of the twenty-eight complete atelectases nineteen were stillbirths and probably never made an attempt to breathe, and, therefore, atelectasis in these cases can not be considered pathological.

An interesting phase of this condition is its association with some intracranial lesion: ten of these atelectatic newborn showed intracranial hemorrhage, and eight congestion of the cerebral vessels (with possible microscopical cerebral hemorrhage). Thus more than 50 per cent. of atelectatic cases showed intracranial lesions.

Ruptured peripheral alveoli with air in the mediastinal tissue extending over the thymus and pericardium in the form of large blebs were found in four cases. The lungs here were completely atelectatic and the injury was probably the result of forcible artificial insufflation or due to oxygen administration under high pressure by the funnel being pushed over the infant's face.

The pleural cavities were found to contain a slight amount of serous fluid in thirty-nine cases, and a large amount of fluid in seven cases. Of the latter, five were bloody, but there were no clots, and showed dark blue hemorrhagic spots on the visceral pleura. Two were clear, serous in character. All these cases showed similar findings in the other serous cavities, and were associated with atelectasis of the lung.

The so-called "asphyxia" spots were observed in five other cases, located mainly on the visceral pleura, and were associated with either intracranial hemorrhage or hemorrhagic disease of the newborn.

The pericardial sac always contained a small amount of serous fluid and in two cases associated with hemorrhage of new-

born and cerebral hemorrhage, bloody fluid was found. The pericardium in three cases of complete atelectasis showed the so-called "asphyxia" spots.

The heart in all cases examined showed a patent foramen ovale. Of congenital cardiac pathology only an interventricular septum defect was found in one case of a six and one half month premature stillbirth. The defect was small and was located at the lower end of the septum.

The thymus was enlarged in seven cases (about 15 per cent.) and this enlargement affected either a single lobe or the entire organ. In one case the entire pericardium was covered by a large right lobe of the thymus which reached down to the diaphragm. In five other cases the thymus showed on section cavities filled with purulent material (DuBois abscess) but none of these showed any evidences of lues. Two normal-sized glands showed hemorrhages in the parenchyma; one was associated with hemorrhage of the newborn and the other with marked congestion in the other organs.

Intraabdominal Lesions.—The abdominal cavity was always found to contain a slight amount of serous fluid, but in eight cases (18 per cent.) the amount of fluid was very great and was associated with a marked vascular congestion. In two it was serous in character and in the other six cases this large amount of fluid was bloody and was divided as follows: four were associated with hemorrhage in other parts of the body, one with syphilis, and one with diabetes in the mother.

The rarest finding in our series was a hematoma of the liver in a full-term baby, born by version and breech extraction. The baby showed pallor for three days and then suddenly died. The abdomen was filled with blood clots, and a search for the source of hemorrhage disclosed a dark blue discoloration under the right diaphragmatic pleura. This was the site of a hematoma the size of a hen's egg in the right lobe of the liver, just under the right diaphragm, with capsule ruptured. The injury occurred at birth, and in the three days enough blood accumulated to cause

the rupture of the capsule. This case was associated with a large thymus and an intracranial hemorrhage and is a strong argument for the early prophylactic employment of blood coagulation tests and blood injections against the hemorrhagic tendencies in the newborn.

In a case of marked icterus neonatorum with no other signs, a very large green-colored liver was found.

The spleen was larger than normal in one case associated with hemorrhages in other organs and on section only showed marked congestion.

Three cases showed hemorrhages in the adrenals. These were always unilateral (two right and one left) the entire gland taking the form of a sac filled with clotted or unclotted blood.

Macerated Skin.—Of eight infants showing maceration or denudation of the skin of various extent, only one was born alive, while the other seven were stillbirths; one of the latter was the premature syphilitic with osteochondritis syphilitica and freely movable costo-chondral junctions; two came from diabetic mothers and showed the most extensive denudation of the skin, involving every part of the body except fingers and toes, and one came from a mother with toxemia of pregnancy.

TABLE V

Hemorrhages in the Newborn

Number of cases	13 or 28 per cent
Premature	2
Full term	11
<i>Location</i>	
Intracranial	7
Single organs	{ 2 thymic 2 adrenal
More than 1 organ but no intracranial	2

Hemorrhagic Tendencies in the Newborn.—Evidences of a so-called hemorrhagic tendency in the newborn were present in thirteen cases, 28 per cent. These evidences consisted of hemorrhages in one or more organs or in one or more serous cavities.

Only two were premature births, while the other eleven were full-term babies, and were associated in seven cases, or in more than 50 per cent., with intracranial hemorrhages; four cases showed hemorrhage in only one organ, these being thymus (2) and adrenal (2). In only two cases were there skin manifestations in the form of purpuric spots. A possible etiologic factor could only be found in three cases: one showing syphilitic osteochondritis, one from a diabetic mother, and the third from a mother with a toxemia of pregnancy.

SUMMARY

1. Intracranial hemorrhage was found in 40 per cent. of our cases, which compares well with the figures of Warwick⁵ and of Bailey.⁶ When we combine these cases with those showing only edema and congestion, we will get a total of 72.6 per cent. showing evidences of intracranial injury.

2. Of the cases with intracranial hemorrhages only 39 per cent. showed hemorrhages elsewhere, a figure much less than Bailey reports (50 per cent.).

3. Fifty per cent. of cases, with evidences of hemorrhagic tendencies, had intracranial hemorrhages, thus supporting the frequent association of these two findings.

4. Hemorrhagic tendencies in the newborn were found in only 28 per cent. of the cases, not as frequently as others report (Warwick 44 per cent.).⁵

5. The frequent association of overriding cranial bones with intracranial hemorrhage was noted in four out of five cases, and the same suggests itself as a possible etiological factor in intracranial hemorrhages.

6. All cases showing cephalohematoma were associated with some intracranial injury, either edema, congestion, or hemorrhage.

7. The finding of a hemorrhage in the lateral ventricle as the only lesion points to the importance of complete autopsies, for, otherwise, lesions of this kind will be missed:

8. The three cases with cord injuries showed only one with an injury to the spine.

9. Fifty per cent. of the cases showing atelectasis were associated with intracranial lesions.

10. Rupture of peripheral alveoli was found in a few cases, and the danger of certain methods of resuscitation was pointed out.

11. The importance of prophylactic measures against hemorrhagic tendencies in the newborn was pointed out in the case with a hematoma in the liver.

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Discussion:

DR. MOENCH: These reports interest me especially, because as Medical Examiner one often has to stretch his imagination almost to the breaking point to determine why a child died. One may get absolutely no history of disease. The child has apparently been perfectly well right along, and when the mother goes to pick it up out of its crib two or three hours later, the child is dead. There has been no vomiting, no diarrhea, no cough, no snuffles; in fact, the more questions one asks, the more one is at a loss to explain why the child should have died so suddenly. In the absence of a diagnosis, an autopsy is performed, but even this frequently does not clear up the case. Sometimes, as Dr. Wilson has noticed in fifteen cases, intracranial congestion and edema are found. But that is no explanation for the death. What are the congestion and edema due to? In some cases nothing at all is found; in others, more or less atelectasis. The microscopical examination fails to clear up the case. We sign out such cases as congestion and edema pending investigation, and have a complete chemical examination done on the brain, liver, and kidneys. Here again, however, the results are usually mostly negative. Other cases are signed out as atelectasis, but why a child who has been apparently well two or three hours previously and has lived with a partial atelectasis for four or six weeks, or even longer, should suddenly die is not very clear. There must be some other factor involved here about which we know nothing.

Such infants as reveal a large thymus are often put down as status lymphaticus deaths, but we must remember that thymus deaths are rather rare in infants, and much more prone to occur in later life.

It is easy enough of course in many cases to determine the cause of death by autopsy if definite findings are present, but when there is a negative history and the autopsy does not reveal anything, it may be utterly impossible to say why death occurred. I would very much like to hear Dr. Wilson's experience in such negative autopsies.

As far as my experience goes, petechiæ are present in many cases, even more frequently on the pericardium, especially the posterior surface, than in any other place. They are also frequent in the heart wall itself.

DR. PIERSON: Atelectasis, like asphyxia, is an unsatisfactory autopsy finding in the newborn as a cause of death. Dr. Wilson spoke of atelectasis as a "lesion." I think that he will agree with me in a friendly criticism of his use of that word, for lesion connotes abnormal anatomy, whereas atelectasis indicates not abnormal anatomy but abnormal physiology. It simply means that the lungs were not aerated, and not that they are not capable of aeration. Many babies are considered to have died from atelectasis, whereas in fact they had large intracranial hemorrhage or other injury to the central nervous system adequate for death. Obviously the lungs of such babies will not be aerated and in a condition of atelectasis.

Dr. Wilson has not defined what criteria he needs for a diagnosis of "hemorrhage in the newborn." Our experience at the Sloane Hospital for Women under the direction of Professor William C. Johnson has been that this condition is rare. We do not classify cases as hemorrhage in the new born unless there are definite mucous membrane hemorrhages or unless an abnormal bleeding and coagulation time have been demonstrated.

In a series of thirty-eight viable babies delivered by the breech and resulting in the death of the babies, fractures of the cervical vertebræ were found in 38 per cent. We demonstrated that over 60 per cent. of these babies showed at autopsy evidences that suggested trauma rather than asphyxia as the primary cause of death. Asphyxia as the cause of fetal death in breech deliveries was found to be responsible in only 5 per cent. of the cases.

DR. WILSON: We have had four negative autopsies in this series. Some of the others showed only congestion and edema of the brain. As I mentioned before, two of these have been examined microscopically, and we found hemorrhages in the medulla, and I think we will find a great number of these with microscopical hemorrhages as a possible cause of death in the negative autopsies.

As to atelectasis, it is true atelectasis is physiological, but most of our cases have been associated with pathological lesions somewhere else, and therefore I included this finding. I did mention that nineteen cases of complete atelectasis never breathed, but some other pathological lesion was found associated with atelectasis in those cases.

In quite a few cases of supposed hemorrhage of the newborn, the coagulation and bleeding time was normal, but we found evidences of hemorrhage at autopsy. We did not find as many as the investigators of St. Louis report. We do not think that all the hemorrhages found belong to the class designated as hemorrhagic disease of the newborn.

The macerated fetus was only partially macerated; it was not complete, and the fetus only lived three quarters of an hour.

BLOOD FINDINGS (CALCIUM AND PHOSPHORUS) IN CRANIOTABES UNASSOCIATED WITH ACTIVE RICKETS *

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Hospital of Brooklyn)*

The literature is replete with blood findings in rickets. The recent chemical work has definitely established an altered calcium and phosphorous metabolism in rickets.

Craniotabes *per se* has received but scant attention. This condition has usually been regarded as one of the clinical findings in active rickets, syphilis, or in osteomalacia.

In the course of the routine examinations of infants in the Feeding Clinic of this hospital, we have found craniotabes to exist in all degrees of severity with either little or no evidence of rickets. This led Wilson and Seldowitz to study these cases clinically in order to investigate in greater detail whether there were present other clinical evidences of rickets, or whether craniotabes existed sufficiently often unassociated with rickets.

These findings are gathered in an unpublished paper where they conclude, supported by clinical, roentgenological and therapeutic evidences that craniotabes does exist without any other evidences of rickets.

The present communication deals with a similar group of cases in which Ca x P concentration in the blood were determined to prove or disprove the clinical conclusions. The appended chart gives the detailed findings.

The cases were selected, and included both breast and artificially fed infants. The investigation extended from March to August, 1923.

These cases were non-rachitic. The outstanding feature in all of them was a marked condition of craniotabes with normal calcium and phosphorus values. It was further found that

* Presented December 13, 1923.

Case No.	Race	Cranio. Age Obs.	Cranio. Age Inv.	Craniotabes	Diet	Rickets X-Ray	Rickets Clinical	Calcium	Phosphorus
821	w.	3 months	6 months	F. 3 x 3 parchment marked occ. parietal	Bottle	Negative	Negative	10.4	4.8
974	w.	7 1/2 "	8 1/2 "	F. 4 x 3 parchment with open sut. parietal	"	"	"		
877	w.	4 "	4 "	F. 2 x 1 marked left temp. par. sl. rt.	Breast	"	Slight bowing	9.41	5.22
1035	w.	6 "	6 "	F. 3 x 3 rt. occ.	"	"	Slight beading	9.23	4.79
1096	w.	5 "	5 "	F. 2 x 1 bilat. parch.	"	"	Slight bowing	10.8	5.42
1093	w.	4 "	4 "	F. 2 1/2 x 2 1/2 marked bilat. par.	Bottle	"	Negative	10.6	4.62
1134	w.	6 "	6 "	F. 2 x 1 marked occ. parietal x 2	Breast	"	Slight beading	10.58	5.46
1155	w.	6 "	6 "	F. 4 x 3 marked occ. parietal x 2	Bottle	"	Negative	10.12	4.75
1061	w.	3 "	3 "	F. 2 x 2 marked rt. temp. parietal	Breast	"	Slight beading	10.64	5.37
1201	c.	2 "	2 "	F. 3 x 3 marked occ. par. x 2	"	"	"	—	4.84
1262	c.	2 "	2 "	F. 3 x 2 marked left occ. par.	"	"	"	10.5	6.21
1294	w.	3 "	3 "	F. — marked rt. occ.	"	"	"	10.6	4.27
912	w.	5 "	5 "	F. 3 x 2 marked par.	Mixed	"	Negative	9.96	4.78
							"	11.9	5.63

these cases of craniotabes, like the craniotabes associated with active rickets, healed rapidly and effectively on exposure to the mercury vapor quartz lamp.

Holt and Howland definitely consider craniotabes a rachitic manifestation. Howland and B. Kramer have shown that the serum of infants suffering from active rickets contains a diminished amount of inorganic phosphorus. If this be true the cases above reported exemplify a type of rickets in which craniotabes was practically the sole evidence of this disease as far as could be determined by all the available methods.

The methods employed in the determination were for phosphorus, a further modification of the modified Bell-Doisy method.¹ Our modification consisted in centrifuging the precipitate for from three to five minutes following the addition of the trichloroacetic acid and then filtering. The Bell-Doisy procedure of filtering the gelatinous precipitate is not only time-consuming and troublesome, but permits appreciably greater evaporation in spite of the watch-glass covers for the funnels. We have found our modification to check well. We have further found in the employment of this method that the filtrates, when well stoppered, kept for at least four days, without alteration in the phosphorous content. This permits of a collection of a number of specimens before readings are made, and is, therefore, a time-saving procedure. For calcium determination, the B. Kramer-Tisdale² method was employed.

Conclusion

A small group of selected cases of craniotabes was studied. Chemically, roentgenographically and clinically these cases failed to show any evidence of rickets.

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2. KRAMER, B., AND TISDALE, F. F.: *Jour. Biol. Chem.*, 1921, xlvii, 476.

Discussion:

DR. WILSON: In this work at our Clinic we studied 164 cases with craniotabes. In 29 per cent. there was rickets. If you take a clinic with any number

of cases at random, you will always find that same number showing rickets as when we took an entire group of craniotabes cases. In other words, we want to show that rickets is incidental in our group, as in any other group of cases. In seventeen cases of very marked craniotabes, only three showed or later developed rickets. We are trying to find out whether craniotabes is really rickets. In some of the cases of craniotabes associated with rickets, cod liver oil was administered for a long while. That influenced the rickets favorably, but the craniotabes was not influenced, or was even increased, again suggesting that craniotabes is probably not the same thing as rickets. With heliotherapy cases of rickets took much longer to show an improvement than cases of craniotabes.

TUBERCULOUS ABSCESS OF THE HEART *

G. L. ROHDENBURG, M.D.

(From the Pathological Laboratories of the Lenox Hill Hospital, New York)

The specimen presented is possibly a novel one. The clinical history of the case is as follows:

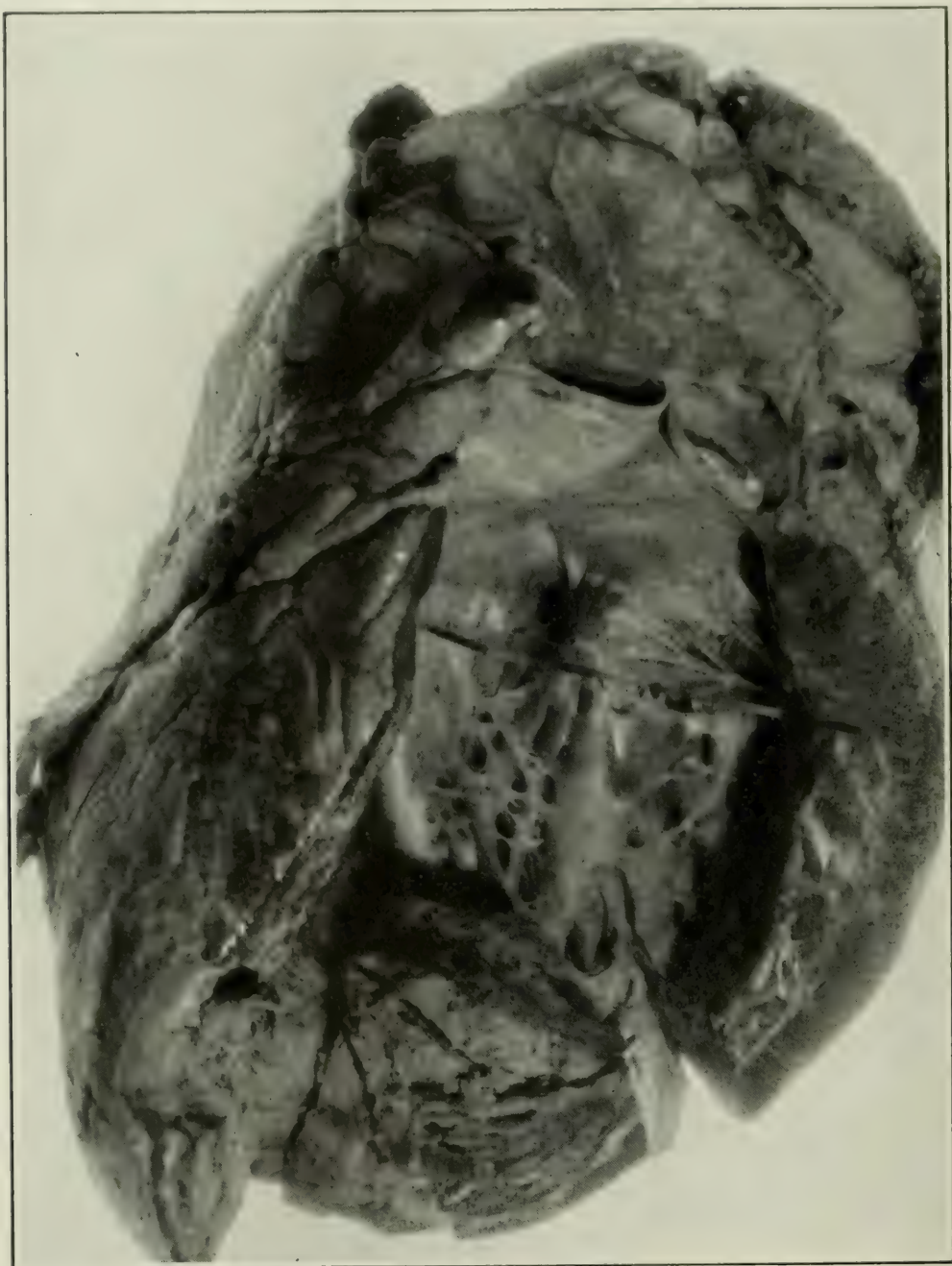
A male, sixty-five years old, a Hebrew, and a tailor by trade, is reported by his family never to have been ill in the past forty years of his life. Six days before death, while playing cards, he suddenly became unconscious, and remained so for about thirty minutes, subsequently recovering consciousness, and stating that he felt well again. He left the card party, walked about half a mile home, and the next morning was found unconscious in the hallway of his home. He was immediately brought to the hospital.

Physical examination disclosed large numbers of diffuse scattered moist râles in both lungs, with evidences of cavitation at both apices. His heart was regular, though the pulse was very weak. No cardiac murmurs were detected. During his stay in the hospital he had a temperature ranging from 100 to 103° F., and during this period he remained unconscious. All examinations of the blood, urine, and spinal fluid were negative. Death occurred very suddenly, without a clinical diagnosis having been made.

The post-mortem examination revealed the following changes: There was a diffuse miliary tuberculosis of both lungs, with cavities of varying sizes and of multiple character in both upper lobes, with also tuberculous involvement of the mediastinal lymph glands, a miliary tuberculosis of both kidneys, spleen, and liver, with active tubercular lesions in the mesenteric lymph nodes. The chief object of interest was the heart. This organ weighed 650 gm. and was distinctly club-shaped with the bulging end at the apex. Upon removing the pericardium there was a distinct bulge of the muscle wall over the lower third of the left ventricle anteriorly, with an appearance suggestive of a pointing abscess. On incision it was found that the lower third of the ventricle wall

* Presented December 13, 1923.

from the ventricular groove in front to within half a centimeter of the groove posteriorly was in a state of coagulation necrosis, and in this area was an abscess containing about 30 c.c. of a thick brownish pus. Sections of the heart wall showed an extensive fibrosis in areas not involved in the coagulation necrosis, and at the edge of the necrotic portions were scattered typical tubercles, while the thrombosed coronary branch vessel was found leading into the



abscess area. Tubercles were also found in the cardiac muscle directly beneath the serosa.

Discussion:

DR. WOOD: Instances of solitary myocardial tuberculosis are much rarer in adults than in children. I have seen several examples of solitary tubercles in children, but none in adults.

DR. SEECOF: Did I understand that there were miliary tubercles in the testes, or was it in the epididymis?

DR. ROHDENBURG: They were in both the testes and epididymis.

THE PATHOLOGY OF PRURITUS ANI, VULVÆ ET SCROTI *

J. F. MONTAGUE, M.D.

(From the Rectal Clinic, University and Bellevue Hospital, New York)

In a definite percentage of cases which present the marked subjective symptom of pruritus we find, in the area to which the pruritus is referred, absolutely no pathological changes in the tissues; on section they present an entirely normal appearance. The explanation of this phenomenon of the lack of histological changes in a cutaneous area apparently the seat of such great functional aberration lies in the fact that pruritus, like pain, may at times be mis-referred and so lead to the apparent discrepancy between local objective signs and local subjective symptoms. This is explained in more detail in my article.¹ In concluding my remarks about the above-mentioned type of case it must be further stated that such a condition is only a transient phase in these cases, for sooner or later, regardless of whether the cause of the pruritus be within the pruritic zone or not, pathological changes in the tissue to which the pruritus is referred *do* develop. This is because of the fact of the scratching which a patient naturally indulges in and which is directed toward the relief of the itching. This scratching itself is a traumatic insult to the tissue and therefore induces a reaction or an infection of the tissues of the pruritic area.

* Abstract of paper presented December 13, 1923.

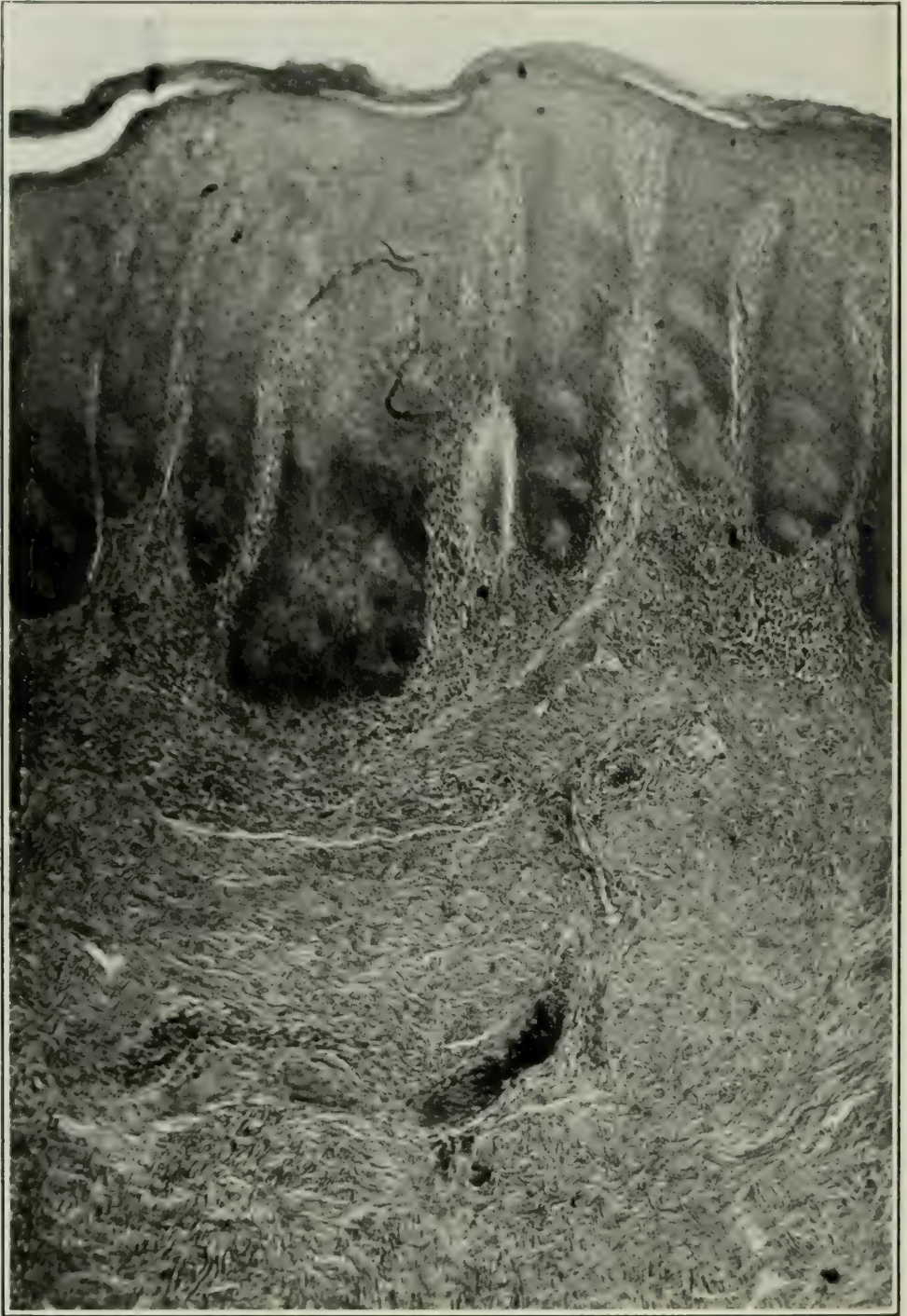


FIG. 1. Anal pruritus of great chronicity but no lesions of the skin evident. *Histological diagnosis:* Chronic productive dermatitis showing hyperkeratosis, hyperplasia of the stratum mucosum, great downgrowth of the interpapillary processes; marked sclerosis of the fibrous connective tissue element of the corium; a tendency toward hyalinization of the epidermal cells. Hematoxylin and eosin stain.

Thus the eventual pathological picture presented is the same in both the mis-referred and the truly referred pruritus. Such changes as are noted fall readily into two main groups to which may be added a third less frequent and from a clinical standpoint less important group.

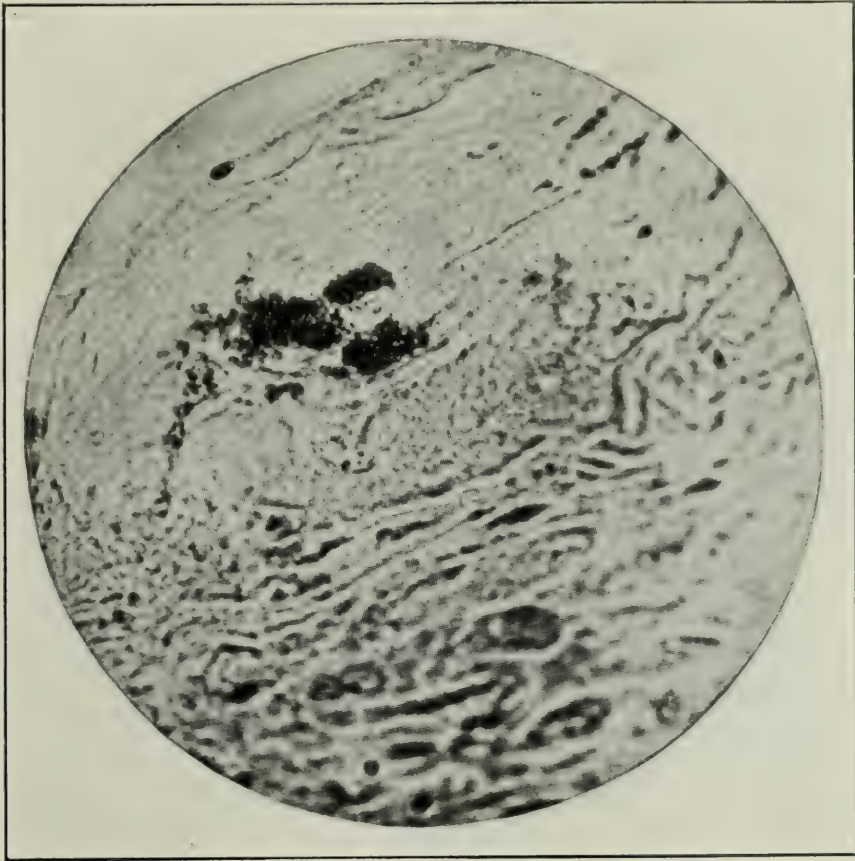


FIG. 2. Bacteria in the epidermal tissue in a case of pruritus ani.

In the first group, a representative of which is shown in Fig. 1, there is an extensive hyperkeratosis, tremendous hyperplasia of the stratum mucosum, great downgrowth of the interpapillary processes; marked sclerosis of the fibrous connective tissue element of the corium and a tendency toward hyalinization of the epidermal cells. In short, we have the picture of a chronic productive dermatitis of traumatic origin. It is absolutely typical of the findings in the majority of chronic cases of pruritus ani, vulvæ et scroti in which no lesions of the skin are evident.

In the second group there is marked pigmentation of the epidermal layers; dilatation of the lymph spaces; diffuse cellular infiltration of the corium which is particularly intense sub-epithelially; some vascular dilation and a general edema of the tissues along with the beginning hyperplasia of the stratum mucosum found in more chronic cases. Briefly, this is the picture of a subacute exudative dermatitis of probable infective origin and frequently is superimposed upon the picture presented in the first group, namely upon a chronic productive dermatitis. Fig. 2 shows bacteria in the epidermal tissues of a case of pruritus. These cases all present, clinically, evidence of skin lesions either in the form of scratches, fissures or erosions all of which breaks in the normal cutaneous barrier to infection render its occurrence inevitable.

The third group of cases is that in which kraurosis has occurred. In cases that have existed for an extremely great length of time (fifteen to twenty years) these changes may occur. They consist in an extensive atrophy of the entire skin in the area affected. This group is a relatively small one as it represents less than two per cent. of all cases. The remainder find classification, as mentioned above, either as a chronic productive dermatitis of traumatic origin or a subacute or chronic exudative dermatitis of infective origin.

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TYPHOID EMPYEMA, WITH REPORT OF A CASE

LUIS AMILL, M.D., AND L. W. FAMULENER, M. D.

(From St. Luke's Hospital, New York City)

The pleural cavity was one of the first sites in which the pyogenic property of the typhoid bacillus was proved. Early studies by French (1885) and German (1887) workers demon-

strated the presence of the typhoid bacillus in pus from purulent pleurisy following typhoid fever. Most medical authorities agree that empyema (suppurative pleuritis) rarely occurs as a complication or sequela of the disease. Occasionally a sero-fibrinous, and more frequently a simple fibrinous, pleuritis appears as a complication, especially when the lungs are involved. Relative to frequency of typhoid empyema, no attempt has been made in this report to collect fully the published statistics, nor to assemble the data on the subject. However, in a brief survey of the literature, only a few large series of typhoid cases were found in which the complications and sequelæ had been analyzed. The statistical results in those series did not closely agree. Osler, in an analysis of 829 cases admitted to the Johns Hopkins Hospital from 1889 to 1899, was able to report only one case of typhoid empyema. McCrae likewise reported in 1907 only one instance of empyema in a series of 1,500 cases of typhoid. Presumably all of his cases were from the Johns Hopkins Hospital, and probably included the earlier group reported by Osler. Reports of similar series of cases in Germany showed a much higher incidence than was shown in the American series. Some evidence exists which indicates that certain epidemics of typhoid fever are followed by a higher percentage of pleural involvements than occur in the ordinary epidemic form. Furthermore, it is possible that the condition is not always recognized during life, as statistics from a large series of autopsies from Munich showed almost 2 per cent. of empyema (McCrae). A decided difference in the incidence of the condition exists between the series reported by the American and by the German investigators. It would appear that empyema has been a much less frequent complication of typhoid fever in this country. Since cases of this character are of rare occurrence, it is desirable that those which do occur be carefully studied and the observations placed on record. Recently the writers had an opportunity to study such a case, and take this occasion to present briefly the main features which may be of special interest.

The patient, a white woman aged forty-nine, and a nurse by profession, was admitted to St. Luke's Hospital, September 12, 1923. The chief complaint was pain, chills and fever. The past history revealed nothing of special importance other than that she had had several diarrhoeal attacks and had not felt well for several weeks preceding the onset of illness. She had been taking care of a typhoid fever patient for two weeks before admission.

Present Illness: Three days before admission to the Hospital she developed marked general malaise, pains in the groin and the small of the back, and mental confusion.

Physical Examination: The patient was a moderately obese woman who did not appear very ill. The temperature was 104° F. (rectal). Her teeth were in fair condition. The tongue was moderately coated. The heart and lungs were negative. The spleen was definitely palpable. A "rose spot" appeared on the abdomen, and two in the middle of the lumbar region. A provisional diagnosis of typhoid fever was made.

Laboratory Examination: On the day of admission a full count showed red blood cells 4,800,000; hemoglobin 91 per cent.; white blood cells 5,900; with polymorphonuclear leucocytes 62 per cent. and lymphocytes 38 per cent. A smear showed no malarial organisms. The first urine showed an acid reaction, specific gravity of 1.010, a faint trace of albumin, acetone and diacetic acid present, and indican negative; microscopical examination showed few leucocytes and many epithelial cells, and debris. On the second day the Widal test with the blood serum in a dilution of 1 : 80 showed very good clumping and impaired motility of *B. typhosus*. A blood culture taken on the same day developed a growth of *B. typhosus*. The laboratory results confirmed the clinical diagnosis of typhoid fever.

Clinical Notes: For over two weeks the disease ran an uneventful course, except for marked delirium and a continued fever of the remittent type which reached a maximum height of 105.2° F. (rectal). Three or four "tubs" were given daily during this period of the disease. On the sixteenth day after admission, the patient complained of pain in the right lower axillary region, but physical examination was essentially negative. On the following day a few fine subcrepitant râles were noted in the lower portion of the right axillary region. The next day frank signs of pneumonia developed. The process involved the right lower lobe posteriorly, but signs of greatest intensity centered at the upper portion of the lobe at the level of the seventh intercostal space and midscapular line. A diagnosis of lobar pneumonia was made. The temperature rose to 105° F., about one degree higher than that of the immediate preceding days. Roentgenograms by portable apparatus made early in the lung involvement failed to show any definite pneumonic consolidation. A blood culture taken when the pneumonia first appeared gave negative results. A sputum collected a few days after the onset of the pneumonia showed pneumococci belonging to group IV. No Gram-negative bacilli were observed. For the ensuing ten days the signs remained more or less unchanged. Fluid was suspected, although no very definite signs were found. The leucocyte counts remained practically unchanged, fluctuating between 5,600 and 8,700, with the polymorphonuclears remaining about 60 per cent. during this period. About

two weeks after the onset of the pneumonic signs, an examination of the chest definitely indicated the presence of fluid. An exploratory thoracentesis was made in the right chest posteriorly in the seventh intercostal space internal to the midscapular line, which yielded about 20 c.c. of fluid. This was seropurulent in nature, brown in color, thick, but on standing a heavy sediment settled. The cells were too numerous per c.mm. to count, but a differential smear showed 99 per cent. of polymorphonuclear leucocytes, and 1 per cent. of lymphocytes. A culture of the fluid yielded *B. typhosus*. A leucocyte count made on the same day as the thoracentesis showed for the first time an appreciable increase, 10,100 leucocytes with 83 per cent. of polymorphonuclears and 17 per cent. of lymphocytes. A second thoracentesis performed the day following the exploratory puncture (at the same point) yielded about 90 c.c. of fluid, similar in nature to that previously described. A few days later the same area was explored, but only 1 to 2 c.c. of blood-tinged, serous fluid was obtained, which might possibly have come from the lung. On culturing this fluid it yielded a growth of *B. typhosus*, and a few diphtheroid bacilli which might come from skin contamination. It was not found necessary to insert a drainage tube, as was originally contemplated for the treatment of the empyema, since the patient recovered spontaneously from the condition. About thirty days after the onset of the empyema, the temperature came down to normal. Two or more consecutive cultures of urine and of stool specimens for *B. typhosus* did not become negative until almost three months after the patient was admitted to the Hospital.

Discussion and Summary: From the bacteriological standpoint, the question arises whether the pneumonia in this patient was due to the pneumococcus or to the typhoid bacillus, or to a mixed infection of the two organisms. It is a question which cannot be fully decided by the data at hand. The sputum submitted for pneumococcus grouping was composed of slightly tenacious mucus, yellow in color, small portions of rusty material, mixed with saliva. The routine examination of the direct smear showed only a few lanceolated diplococci and a very few Gram-positive bacilli, but no Gram-negative bacilli were found. Culture of the selected clumps of this specimen in Avery's medium yielded several forms of organisms, including Gram-positive oval cocci in medium to long chains, Gram-positive cocci in clusters, and a few Gram-positive bacilli; again no Gram-negative bacilli were observed. The bile test showed a fair lysis, only relatively few pneumococci were present; these were found to belong to type IV by the usual specific precipitin tests. It is difficult to exclude the saliva as the source of the pneumococcus in this case, since

that organism commonly occurs in the mouth. Possibly the fluid which was obtained in the last exploratory puncture of the chest came from the lung tissue proper in the affected portions. It yielded *B. typhosus* on culture, but no pneumococcus, although the latter organism might have been eliminated from the involved lobe at that stage of the healing process. On the other hand, in passing the exploratory needle to the lung, a previously infected pleura had to be passed, and might infect any materials which came from the lung tissue. Neither of the cultures of the pus from the pleural sac yielded the pneumococcus, which is in favor of a typhoid infection of the lung.

From the clinical standpoint, this case is an illustration of a self-limiting process, with recovery from empyema without operative interference. It would appear that the patient had a well-established immunity which overcame the complication before it progressed to a chronic condition.

The writers wish to acknowledge their indebtedness to Dr. Samuel W. Lambert, Director of the Medical Service, St. Luke's Hospital, for permission to report this case.

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THE VALUE OF EXAMINING BODY FLUIDS FOR TUMOR CELLS *

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The literature pertaining to this subject deals chiefly with the finer points of cellular pathology, such as mitotic figures, specific degenerations, disturbed nucleo-cytoplasmic relationships and atypical formations, etc., which are urged as differential characteristics between cells derived from malignant and non-malignant tissues, or to isolated conditions in which tumor cells or masses may be found in body fluids.

In this communication, no attempt is made to suggest any new method which might enable one to discriminate between "malignant" and "non-malignant" cells; but, by an analysis of the material collected we will try to show what may be the possible value of a routine method of examining for tumor cells the fluids from cases in which there exists the slightest possibility of malignant disease.

The procedure for a long time followed in the Montefiore Hospital Laboratories has been to fix the specimen in Orth's solution, and to embed the centrifuged sediment in paraffin. The cut sections are stained with hematoxylin and eosin. The microscopical report of such a section would but in a small measure de-

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pend upon the skill of the examiner, for usually clumps of easily recognizable tumor cells, or numerous highly irregular cells with mitotic figures or disturbed nucleo-cytoplasmic relationships, and so forth, in general, highly atypical cells, would help to make the diagnosis fairly simple.

An investigation of the value of such routine examinations was undertaken because of the interesting findings in several instances. In one specimen the recognition of tumor cells in the pericardial fluid gave the first clue toward the diagnosis of intrathoracic neoplasm. Clinically, this case at the time was diagnosed serofibrinous pericarditis, and even at autopsy the diagnosis of malignancy could not be made in the gross,—the tumor was of a miliary type in the lymphatics of the pleura, and had invaded the pericardium secondarily. Again, in a pleural fluid from a case clinically diagnosed pulmonary neoplasm, the type cell suggested the possibility of an endothelioma of the pleura and the diagnosis was corroborated at autopsy.

To determine whether such fine results could be obtained constantly and under controlled conditions a study was made of fluids from many sources, regardless of whether the cases were suspected of malignancy, by the examination of all fluids which reached the laboratory for other purposes and by the cooperation of the clinical residents. Thus many known negative fluids were included to serve as control specimens. How pertinent this question was, became evident very soon by several instances in which tumor cells were reported in fluids from cases which later proved to be non-malignant. Among such, was an abdominal fluid in which the highly atypical cells were reported as tumor cells in a case which at autopsy showed no malignancy. Again, a pleural fluid was reported positive for tumor cells in September, 1922, but the patient improved, left the hospital and is still alive. Likewise, "cells resembling those of a hypernephroma" were reported in November, 1921, in a sinus discharge from a patient who is still alive with no symptoms of a malignant disease.

This report therefore consists of an analysis of the findings in 97 cases from which 142 specimens were examined routinely.

Fluids which others had reported were reexamined; and where different observers disagreed, my own (S.) is given to make the findings "constant" in so far as the errors of the examiner are concerned. Several specimens from proved malignant cases were reviewed and the tumor cells were found in fluids previously reported negative.

The results were grouped under the heading positive, negative and questioned, according to whether the specimens respectively revealed, or were free from tumor cells, or contained atypical cells which could not be classified.

Table I shows the distribution of the 142 specimens according to the source of the fluids, and a comparison of the microscopic reports checked against the clinical diagnosis at the time

TABLE I

Comparison of Microscopic Findings with Clinical Diagnosis at Time Specimen was Received

Source of Specimen	Totals	Positive		Negative		Questioned	
		Micro.	Clin.	Micro.	Clin.	Micro.	Clin.
Pleural fluid.....	64	21	23	32	26	11	15
Abdominal fluid.....	39	17	25	13	12	9	2
Sputum.....	19	4	11	14	7	1	1
Gastric contents.....	9	3	5	6	4	0	0
Brain cyst.....	2	2	2	0	0	0	0
Spinal fluid.....	1	0	1	1	0	0	0
Sinus discharges.....	3	1	2	2	1	0	0
Stool.....	2	0	0	2	2	0	0
Urine.....	1	0	0	0	1	1	0
Hydrocele fluid.....	1	0	0	0	0	1	1
Pericardial fluid.....	1	1	0	0	1	0	0
	142	49	69	70	54	23	19

the specimen was received. Thus, the fluids were reported positive 49 times against 69 positive clinical diagnoses or 71 per cent., 54 times negative against 70 negative clinical diagnoses or 50 per cent., and 19 against 23, or 83 per cent. questioned. The point to be noted is that the microscopic examination was positive less often and negative more often than the clinical diagnosis.

Since the clinical diagnoses in the cases with more than one specimen may have varied with each specimen, and the microscopical reports of several fluids from the same case may have varied with each specimen, and frequently the diagnosis (especially at autopsy) may have disagreed with either the clinical or microscopical diagnoses, or both, it became necessary to check the microscopical findings against the final outcome of the case. The cases were analyzed in two groups: (a) the total 97 cases which, according to the autopsy, the final diagnosis at death or discharge, or the clinical diagnosis at present, were grouped as positive, negative or questioned cases and (b) 40 cases whose outcome was determined by autopsy or biopsy.

Of the 97 cases, 74 gave single specimens and of the remaining 23, 16, more than one specimen from a single source. By combining the 7 cases with specimens from more than one source with the few odd specimens into a miscellaneous group, the cases were readily tabulated according to the source of the fluids as shown in Table II. (When one of several specimens from the

TABLE II

Agreement in 97 Cases Checked against the Final Diagnosis or Autopsy

Cases	Pos.	Neg.	?	Total	%	Single Specimen Cases
38 Pleural fluids.....	15	12	3	30	79	34
23 Abdominal fluids.....	10	4	1	15	65	15
12 Sputum examinations.....	3	4	1	8	75	9
8 Gastric contents.....	2	3	0	5	62	8
16 Miscellaneous.....	6	3	2	11	69	8
97	36	26	7	69	71	74

same source was positive or questioned, the microscopical report on the case was taken to be positive or questioned respectively.)

Summarized, this table reveals that agreement occurred in 36 positive, 26 negative and 7 questioned cases, or 69 out of 97, or 71 per cent.

In the series of 40 cases whose outcome was determined by

autopsy or biopsy, agreement occurred in 22 positive and 7 negative, or 29 out of 40 cases, or again 71 per cent.

TABLE III
Agreement in the 40 Cases Checked by Autopsy or Biopsy

Cases	Positive	Negative	Total	%	Single Specimen Cases
20 Pleural fluids	12	3	15	75	14
9 Abdominal fluids	6	1	7	78	6
6 Sputum	1	1	2	33	2
1 Gastric contents	1	0	1	100	1
4 Miscellaneous	2	2	4	100	4
40	22	7	29	71	27

In Table IV is shown the manner of disagreement in 11 out of the 40 cases of the autopsy series :

TABLE IV
Manner of Disagreement in the 11 of the 40 Cases Checked by Autopsies or Biopsies

Micro. Report	Total	Type Case	Autopsy or Biopsy	Single Specimen Cases
Positive	2	{ 1 Pleural fluid	Neg.	1
		{ 1 Abdominal fluid	Neg.	
Negative	6	{ 2 Pleural fluids	Pos.	2
		{ 4 Sputum	Pos.	2
Questioned	3	{ 2 Pleural fluids	Pos.	2
		{ 1 Abdominal fluid	Pos.	
	11			7

(For the purpose of this communication, it was deemed unnecessary to analyze the 28 disagreed cases of the 97. It might be mentioned, though, that six were reported positive which proved to be negative or questioned, 16 reported negative were positive or questioned, and 6 reported questioned were positive or negative.)

DISCUSSION

It is well known that the body fluids from cancer patients may contain tumor cells and sometimes grossly visible tumor masses. In the absence of the latter, our results indicated that in 71 per cent. of cases fairly accurate diagnoses may be made by a routine microscopical examination of fluids for tumor cells. The importance of this lies in the fact that such specimens are easily available; and that the findings may be of value in ruling out, confirming, and sometimes aiding in, if not alone establishing, a clinical diagnosis of malignancy.

Within the last ten years, 34 cases of primary lung tumors have come to autopsy at the Montefiore Hospital, 23 since 1918. (It was in connection with these cases that the clinicians would send pleural fluids and occasionally the sputum to be examined for tumor cells.) Within the same period, the literature of all countries records a marked increase in cases with pulmonary neoplasms. Today, no doubt, malignant tumors of the lung are looked for more diligently and diagnosed more often. Yet, many case reports state that clinically the true condition was not recognized until late, if at all, in spite of repeated negative examinations for specific diseases and in the presence of unusual symptoms and physical signs. The opinion is ventured that the diagnosis might have been established in some of the missed cases if the specimens of sputum or pleural exudates which were repeatedly obtained, but were discarded or examined only for bacteria or other specific elements, had been examined for tumor cells. And again, when upon physical examination malignancy is suspected, in the absence of facilities for confirmation, such as *x*-ray studies, bronchoscopic examinations or biopsies, a study of the available fluids may be of some aid in confirming the diagnosis.

What has been said concerning pleural fluids and sputum for intrathoracic tumors may be applied to any fluid, which, because of its proximity to the malignant growth, may contain the tumor cells.

A few practical suggestions concerning this method may be

mentioned: (1) Tumor cells may be recognized in rare instances in ordinary smear preparations when the examiner is on the alert for them.

(2) Of the 97 cases studied, there were 74 in which a single examination was made. It is evident that the search for a few possible tumor cells in a large amount of fluid presents the same difficulties that are encountered in the examination for bacteria under similar conditions, or for small foci of malignancy in organs or large tissue specimens. Serial sections are not necessary, and the probabilities of a correct diagnosis in both positive and negative instances are increased by examining repeated specimens—when available.

(3) Unlike bacterial examinations, in the absence of a specific stain for tumor cells, these cannot be entrusted to persons who are not familiar with at least the general microscopic characteristics of malignancy. Great care should be exercised in designating as malignant those highly atypical cells found in long standing pleural or peritoneal effusions. This point has been emphasized by many and perhaps partially explains the infrequent recourse to this method even in suitable cases.

(4) The presence of tumor cells in a fluid from a given source does not always indicate that the primary focus of the disease is in the neighboring organs. That the cells may reach the fluid from a metastatic focus is to be borne in mind since the primary site may be unrecognized or have been removed previously.

(5) Finally, a malignant tumor may exist in the presence of other conditions, so that the search for tumor cells should not be abandoned upon finding tubercle bacilli in the sputum, pus in the pleural fluids and so forth, in clinically atypical cases, especially in elderly people.

SUMMARY

In fluids which might contain them, the presence of tumor cells may be detected in about 70 per cent. of cases by a simple routine procedure. When the results are taken in conjunction with careful and complete clinical studies such examinations may

be of great value in proving and establishing the diagnosis of malignancy.

CONCLUSION

Because any procedure which may help to make the diagnosis of malignancy early or definite is of distinct value in deciding the prognosis and proper treatment of suspected cancer cases, it was thought worth while to point out the possible aid which may be derived from a routine examination of body fluids for tumor cells.

ON THE ENLARGEMENT OF THE THYMUS FOLLOWING SUPRARENALECTOMY *

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(From the Division of Laboratories, Montefiore Hospital)

We wish to present experimental data in support of an interrelation that has been suspected for some time from clinical and pathological studies. Among the earlier reports on Addison's disease frequent mention is made of the association of a large thymus with diseased suprarenals. With the accumulation of considerable data upon this disease the association becomes more constant and significant.

Detailed and convincing experimental evidence of thymic enlargement following suprarenal injury or ablation could not be found in the literature. We have not been able to find any studies dealing specifically with this point. Boinet and Calogero, working with rats, and Auld, working with cats, have mentioned thymic enlargement following suprarenalectomy, but since most of their animals died within two days after removal of the second gland the changes they described could hardly be due to suprarenalectomy. In addition, they knew neither the ages nor the life histories of their animals, nor did they have proper controls, and their conclusions in this respect are, therefore, open to serious criticism. Crowe and Wislocki, in 1914, while studying the

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effects of suprarenal ablation in dogs, observed enlargement of the thymus in four animals that survived in good condition subtotal extirpation of these glands for from two weeks to six months. Marine and Baumann, and Scott, in studies on suprarenal insufficiency in rabbits and cats, have also observed hyperplastic thymuses in those animals that have survived in good condition for long periods of time removal of both glands.

Our work on the rat is the first in which thymic enlargement following suprarenalectomy has been observed and studied in a large series of animals. By the use of operated and non-operated controls, together with the tables for the normal rat as compiled by Donaldson, we have demonstrated this change objectively. The strain of animals studied was the same as that used by Donaldson of the Wistar Institute, that is, very tame white rats. They were raised and interbred in the Laboratory and their exact ages were known. All of the animals were kept under the same physical and nutritional conditions. These factors are of primal importance in any research involving the thymus, for the gland is subject to a tremendous, although to a considerable degree controllable variation. Wistar rats offer an additional advantage in that growth and development curves for the body as a whole and for the various organs have been tabulated for large numbers of animals as kept under standardized conditions at the Institute.

We have summarized our experimental data in two tables. The first (see Table I) separates our animals into two groups, namely, those which died after removal of both glands, and those which were killed by vaccine or sacrificed. Seventeen animals which died within two days following suprarenalectomy are tabulated. The weights of their thymuses averaged 0.155 gm., while the weight of the thymuses of 17 animals of the same age as given by Donaldson would average 0.201 gm. Our average is therefore 23 per cent. below Donaldson's for animals of the same age. We have also sacrificed some normal animals in good condition and compared the weights of their thymuses with Donaldson's standards for the same ages and have found that our non-operated

normals average 25 per cent. to 30 per cent. in weight below the Wistar standards. The fact that the weights of our normal thymuses are about 30 per cent. below Donaldson's is easily explicable on the basis that our animals were kept under different physical and nutritional conditions. We have included the thymuses of animals dying within two days after suprarenal-ectomy with those of our normal, sacrificed controls; these groups represent the average difference between our figures for normal and Donaldson's. We have done this because two days is insufficient time for detectable hyperplastic changes to manifest themselves.

TABLE I

	Days after Supra- renal- ectomy	Cause of Death	Num- ber of Rats	Average Normal Weight of Thymus (Donaldson), Gm.	Average Weight of Thymus (autopsy), Gm.	Per Cent. Difference from Donaldson
Died	1-2	Acute P.O.	17	0.201	0.155	- 23
	3-4	" "	5	0.244	0.177	- 27
	5-6	" "	8	0.234	0.134	- 42
	9	Prog. Insuff.	1	0.186	0.220	+ 18
	14	" "	1	0.220	0.169	- 23
	25	" "	1	0.203	0.103	- 49
	29	" "	1	0.199	0.113	- 43
Killed or Sacrificed	9	Vac. Injec.	3	0.182	0.207	+ 13
	12	" "	1	0.175	0.235	+ 37
	22	Struggling	2	0.148	0.334	+ 120
	29	Fighting	1	0.288	0.375	+ 30
	35-40	Sacrificed	2	0.123	0.248	+ 98
	65-75	"	4	0.144	0.202	+ 40
	80	"	1	0.124	0.193	+ 55
	170	"	1	0.085	0.160	+ 88
	210	"	4	0.086	0.096	+ 11

Showing animals which died after removal of both glands and those which were killed or sacrificed at varying periods after suprarenalectomy. Their thymuses are compared with Donaldson's standards.

Five animals dying within 4 days after operation had thymuses 27 per cent. below the Wistar figures, while 8 dying within 6 days showed thymuses 42 per cent. below these figures. This low figure is due, we believe, to an additional factor, namely, that suprarenalectomized rats moribund for some days do not take

food, and thymus involution due to inanition is manifesting itself. One animal dying of progressive insufficiency 9 days after operation had a thymus 18 per cent. above the Wistar figures. We cannot explain this except on the basis of physiological variation. Its thymus may have been very large at the time of operation. Another rat dying 25 days after suprarenalectomy from progressive insufficiency with marked loss of weight presented a thymus 49 per cent. below the Wistar figure for the same age, while one dying 29 days after suprarenalectomy was 43 per cent. below Donaldson's figures.

We pass now from these animals, of which 33 out of 34 showed thymuses much below the Wistar standards, to rats that were killed by vaccine or sacrificed from 9 to 210 days after suprarenalectomy. One is immediately impressed by the remarkable difference shown when their thymus weights are compared with Donaldson's standards for the same ages in normal rats. All these animals had thymuses above Donaldson's standards. Three were killed 9 days after suprarenalectomy by vaccine; they were in good condition at the time of injection and would probably have survived indefinitely. Their thymuses were 13 per cent. above the Wistar standards. Two others died shortly after bleeding from the tail, death being due to handling and struggling. Their thymuses averaged 120 per cent. above the Wistar standards. Two were sacrificed 35 to 40 days after operation, their thymuses were + 98 per cent. Four rats had thymuses which averaged + 40 per cent. at 65 to 75 days after operation. At 170 days one rat had a thymus of + 88 per cent. and at 210 days 4 rats had thymuses averaging 11 per cent. above the Wistar standards.

When our figures are corrected on the basis that our normals are about 30 per cent. below Donaldson's standards, then the changes become even more significant in that thymuses that averaged + 11 per cent. become + 44 per cent., while those that averaged + 120 per cent. become + 186 per cent.

Table II shows 7 suprarenalectomized animals that lived for from 22 to 170 days after operation. Each rat is compared with

an age, or approximate age, control. This brings out clearly the difference between the thymuses of some of the operated animals and their age controls.

TABLE II

Number	Sex	Age at Death	Wt. at Death	Cause of Death	Duration of Life after Supra-renal-ectomy	Wt. of Thy-mus	Wt. of Thymus (Donald-son)	Per Cent. Differ. from Donald-son
		Days	Gm.			Gms.	Gms.	
RW 16-3....	F.	218	185	Struggling	22	0.313	0.148	+ 110
RW 17-4....	M.	210	245	Sacrificed	Control	0.155	0.142	- 9
RW 16-2....	F.	218	155	Struggling	22	0.355	0.148	+ 140
RW 26-3....	F.	196	153	Acute P.O.	1	0.140	0.167	- 16
RW 3-2....	M.	87	160	Fighting	29	0.375	0.288	+ 30
RW 8-1....	M.	95	167	Acute P.O.	1	0.240	0.273	- 12
RW 20-4....	F.	264	200	Sacrificed	41	0.186	0.113	+ 65
RW 31-2....	F.	274	230	Acute P.O.	2	0.115	0.108	+ 8
RW 16-1....	F.	261	295	Sacrificed	65	0.200	0.115	+ 74
RW 31-1....	F.	263	202	Acute P.O.	2	0.112	0.113	0
RW 17-1....	F.	210	225	Sacrificed	67	0.225	0.155	+ 45
RW 26-4....	F.	196	152	Acute P.O.	1	0.092	0.167	- 45
RW 9-3....	F.	306	255	Sacrificed	170	0.160	0.085	+ 88
RW 11-4....	M.	306	330	Sacrificed	Control	0.098	0.085	+ 15

Showing animals which have survived double suprarenalectomy for varying periods. Their thymuses are compared with those of age or approximate age controls.

In the detailed study of our data we have found that removal of the suprarenals will accelerate the growth of the thymus during its normal growth period, while during the period of involution it will bring about regeneration and reactivation of the gland, and finally when regeneration has taken place the normal involution is delayed even as long as six months after the operation, provided, however, the animals do not develop parasitic skin diseases, snuffles or snuffle pneumonias, or lose weight from any other cause. This involution is of course pathological. If, however, the insufficiency is entirely compensated by regeneration of

fragments of suprarenal left behind at operation or by marked hypertrophy of accessories, then involution of the thymus will progress normally.

We have studied our tissues histologically using paraffin imbedding, and staining with hematoxylin and eosin. The most striking change is a thickening of the cortical zone with marked preponderance of the small round thymic cells of the lymphocytic type. Microscopically, the thymus of a suprarenalectomized animal 200 days of age may appear like that of a normal 70 day rat in which the thymus is growing actively.

We will not enter into a detailed discussion as to the mechanism involved in the hypertrophy and hyperplasia of the thymus following removal of the suprarenals. The enlargement may be an expression of the generalized lymphoid hyperplasia that follows suprarenalectomy, and which is characterized by the appearance of the prominent lymphoid foci in the various organs, including the heart and thyroid, a generalized hyperplasia of the lymph nodes and bone marrow with the appearance of a lymphocytosis. On the other hand, the thymic enlargement may be effected through the gonads and parasex tissues. We are well acquainted with the close association between the gonads and suprarenals. The suprarenals undergo enlargement in pregnancy, ovulation, and castration. The ovaries hypertrophy after suprarenalectomy. Tumors of the suprarenals are associated with sex perversion and virilism in the female and male. The interrelation between the gonads and the thymus is also well known.

The following is an attempt to correlate our experimental findings with some of the clinical conditions in which the thymus is enlarged.

I. *Addison's Disease*: In this disease, enlargement of the thymus is a very common autopsy finding. If pathological involution could be excluded it is quite possible that this change would be noted in nearly every case. It is not our intention to enter into a discussion as to whether changes in the interrenal or chromaphil portions of the suprarenal gland, or both, are the

basis of this disease. In any event, the association of an enlarged thymus with diseased suprarenals is very interesting.

2. *Graves' Disease*: About 95 per cent. of the cases of fatal Graves' disease coming to autopsy have large thymuses. Non-fatal cases present varying degrees of thymic enlargement. Marine has for a long time insisted upon the participation of the suprarenal gland in the production of clinical Graves' disease. Marine, Baumann, and Scott have reported prolonged rise in heat production in rabbits and cats made insufficient by sublethal suprarenalectomy, but surviving the operation in fair condition. May not the enlarged thymus of Graves' disease be in part dependent upon the lymphoid state induced by functional involvement of the suprarenals in this disease?

3. *Status Thymicolymphaticus*: We should be cautious about generalizations, but it is known that suprarenalectomy induces a lymphoid state characterized by the appearance of lymphoid foci in various organs; enlargement of the thymus, hyperplasia of the lymph nodes, and Peyer's patches; the appearance of a lymphocytosis, a marked diminution of resistance to infections and intoxications, severe reactions following the injections of alkaloids and antigens and frequently sudden death incidental to struggling. These are also the cardinal evidences of status thymicolymphaticus.

Discussion:

DR. PAPPENHEIMER: Dr. Jaffe has filled up an obvious gap in our knowledge of the relationship of the thymus to the suprarenals by his experimental demonstration that hyperplasia of the thymus regularly follows suprarenal extirpation. The thymus is a difficult organ to work with, because it is so subject to nutritional influences. I should like to ask a few questions: Were the animals operated on before sexual maturity, and could it be determined whether there was a delay in the normal involution of the thymus following suprarenalectomy, or whether, as seems to be the case in some instances of Graves' disease, a renewal of growth occurred after the onset of the condition? What was the general state of nutrition of those animals which survived operation for a long time? How did their body weight and nutrition compare with the normal animals of the same age? The thymus very accurately reflects the general nutritional state, and I wondered whether possibly some of this hyperplasia might not be accounted for by the fact that these animals were less active than normal animals, and put on weight. It is pos-

sible that the thymic enlargement is not necessarily evidence of a direct correlation between two organs of internal secretion, but merely an expression of a better state of nutrition.

DR. MOSCHCOWITZ: I should like to speak about the relation of the thymus to Graves' disease. Most recognize some relation, and many hypotheses have been submitted to explain this relationship. It seems to me that the problem is not so difficult if we attempt to correlate certain clinical facts with the pathological. The conventional theory presupposes that a hyperplasia of the thymus occurs as the result of the Graves' disease. I do not believe that as yet anybody has shown that a thymus gland which has undergone the usual changes associated with involution can undergo an hyperplasia to the great degree witnessed in patients with Graves' disease. Indeed, it would be a difficult problem to prove. I do not believe that it can occur, for I do not see how a tremendously hyperplastic thymus can arise from mere shreds of fat, fibrous tissue, and the few thymic cells. My belief is that a hyperplastic thymus represents a persistent thymus and nothing else. Moreover, nobody has ever taken into consideration the hyperplasia of the remaining lymphatic apparatus of the body. Does this also develop into Graves' disease? Now in studying the histories of patients with Graves' disease two facts can usually be determined: first, there is a history of long-standing neurosis, sometimes dating to childhood. This is often familiar and is of various types. Most often it is an anxiety neurosis. Usually such patients are extraordinarily sensitive. Sometimes it is a constitutional inferiority; sometimes ordinary psychasthenia. Second: There is a history of a shock or psychic trauma just preceding the onset of the Graves' syndrome. This is sometimes a fever, a robbery, the death of a parent, a preceding infection. It is well known that after the Ring Theatre fire in Vienna and after the San Francisco earthquake there was a sudden increase in the number of patients with Graves' disease. Now it is well known that patients with status lymphaticus are constitutionally inferior. They are neurotic, sensitive folk, and most susceptible to both physical and especially psychical insult. It seems to me therefore that the explanation of thymic enlargement in Graves' disease is this: patients with status lymphaticus are merely susceptible subjects for the onset of Graves' disease, as the result of psychic shock.

DR. PLAUT: The material presented is very interesting in adding something to the question of the nature of the round cells of the thymus. After suprarenalectomy the round cells of the thymus show a marked increase, and at the same time in other organs lymphoid foci are to be made out. If it can be determined that the round cells of the thymus and the cells of the lymphoid foci in other organs, as in the thyroid and the heart muscle, have the same character, this would be one argument in favor of the theory of many authors that the round cells in the thymus and in the lymphoid foci really are identical. Another thing which would be interesting to do in experiments like this is to study the histological picture of the different organs, especially of the other endocrine organs, because studying the relationship between two endocrine organs is difficult if we do not know the condition of the others, since they are all so closely connected.

DR. JAFFE: In answer to Dr. Pappenheimer's questions, most of the animals which survived double suprarenalectomy for a long period of time were operated on when they were five or six months of age. They were sexually mature. We assumed that the thymuses of these animals were undergoing involution, which I understand begins about seventy days of age in rats.

Considering the question of whether the thymus enlargement in these animals could be due to improved nutritional conditions or to marked increase in weight, most of the animals which presented large thymuses, and particularly those which had thymuses 120 to 130 per cent. above Donaldson's averages, showed a loss of weight of from 10 to 15 per cent. shortly after operation, which may not have been regained at the time of death. We have seen animals which were eating much more than normal animals and still at the end of two weeks weighed less than they did at the time of operation. Some of the animals which we sacrificed from four to ten weeks after operation had regained the weight that they had lost, and were heavier than at the time of operation, but the increase in weight which they showed was not any greater than the increase which control animals would show during this period of time. On the whole, I believe that the weights of these suprarenalectomized animals were less than those of normal animals of the same age. We have taken the factor of nutrition into consideration, and we were impressed by the fact that the thymus may be enlarged following suprarenalectomy, although the animal is gaining very little weight, provided, however, it is eating.

DR. PAPPENHEIMER: Have you figured out the ratio of the thymus weight to the total body weight?

DR. JAFFE: No, but we compared the weights at operation and a week, ten days, and two weeks after operation, and so on all during the course of the experiments. Most of the animals that we sacrificed were in good condition at the time. Clinically, we could not tell the difference between the operated and the controls.

Concerning the discussion of Dr. Moschowitz, I cannot say much, but I suppose that the anlage of Graves' disease is present before the syndrome manifests itself, and possibly the thymus is enlarged in these cases because of a disturbance in the functions of the suprarenal glands. I do not know whether there may be complete reactivation of thymuses that have gone on to complete involution. I understand that the thymic changes in Graves' disease consist essentially in thickening of the cortex and prominence of the lymphocytes.

Concerning the question about the cells in the various organs, they were not studied in detail. Dr. Marine has observed these changes. He has seen small nests of cells of the lymphocytic type, and he has told me that in the thyroid gland they are very prominent.

A CASE OF GAUCHER'S DISEASE *

ELI MOSCHCOWITZ, M.D.

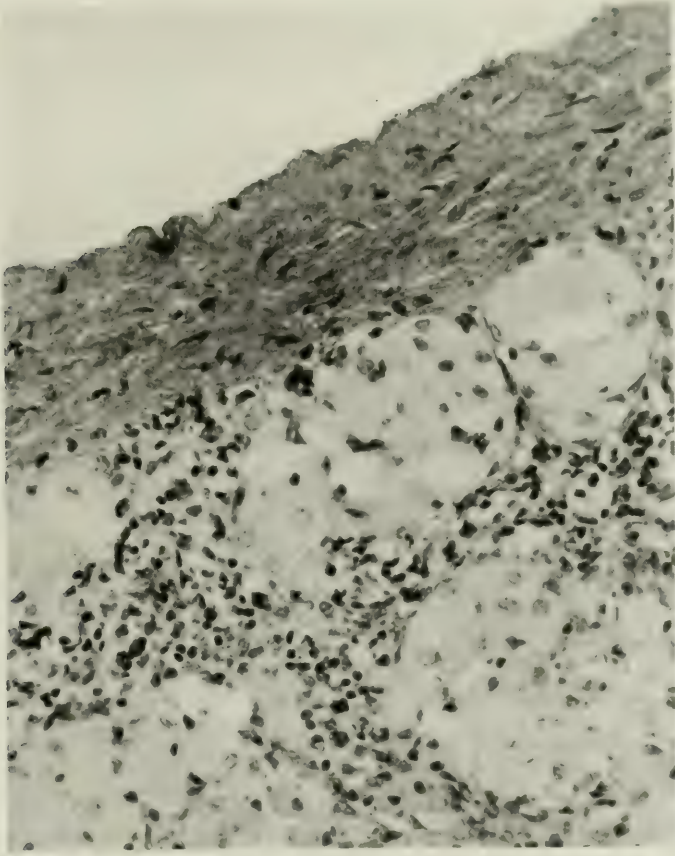
My purpose in presenting this case is simply to add another to the records of this rare disease. The clinical and pathological findings have been so thoroughly elucidated by Brill, Mandlebaum, Libman and Downey that I can add nothing new to their observations. Furthermore, the history of the disease in this instance is quite remarkable.

R. R., a girl, aged fifteen, was admitted to Beth Israel Hospital on December 19, 1922, with signs pointing to an osteomyelitis of the right femur. She had complained for four days of pain in the right knee, and there was swelling and tenderness in this region. She had a temperature of 101° F. Her leucocyte count was 10,000, of which cells 78 per cent. were polymorphonuclears. The following day an osteotomy was done. The periosteum was found elevated with old blood; the femur was explored, but no pus was found. A diagnosis of hemorrhagic osteomyelitis was made. The patient was discharged on January 16, 1923, with an open sinus. She was re-admitted on February 16, 1923, because of pain, redness and swelling of the right thigh. The temperature varied between 100° and 102° F. There was a secondary anemia, with the red cells 3,200,000; hemoglobin 55 per cent., and leucocytes 5,600. The polymorphonuclears were 53 per cent. On February 10th the medullary cavity was found filled with necrotic bone and an abscess of the popliteal space was drained. She continued to have fever, and on June 6th a sequestrum was removed. Two days later she complained of sharp pain in the left side of the abdomen. The left upper quadrant was tender and rigid, and at that time there was noted an enlarged spleen which was tender and extended to Poupart's ligament. There must have been splenic enlargement before this but the history is silent on this point. On June 21st the red cells were 1,600,000; hemoglobin 33 per cent., and leucocytes 6,900, with polymorphonuclears 90 per cent. A transfusion was done. The fever persisted. On August 27th a splenectomy was performed. The patient is well to-day.

The spleen measures $21 \times 12 \times 10$ cm. and weighs 1,940 gm. The surface is covered by old tough adhesions; the capsule is tense, but not thickened. On the upper third and middle of the anterior edge are two rather large infarctions. The upper is superficial and penetrates about 1 cm. into the substance. The lower penetrates about 3 cm. Both are firm and show no softening. About the mid portion of the convex surface are two smaller infarctions, each about the size of a marble, which have the same physical

* Presented January 10, 1924.

characters as the former. On section, the organ is firm and beefy red. The cut surface springs forth slightly from the capsule. Throughout the organ are a number of smaller and larger circular and sharply defined hemorrhagic areas varying in size from a pin-point to a hazelnut. At the hilus a small abscess holding about a drachm of pus was opened. This contained *Streptococcus hemolyticus*.



The lymph gland in the hilus shows abundant Gaucher transformation.

Microscopically, with the low power, the characteristic Gaucher picture as described by Mandlebaum is noted: the circular splenic sinuses partially or completely filled with the pale, faintly staining "lipoid" appearing cells with a thin framework of normal splenic parenchyma between. The majority of the sinuses are filled with these cells with the exception of spaces usually at or near the center, which contain red blood cells. Others show the characteristic spaces lined along the periphery with Gaucher cells with a fairly large central space containing red cells, resembling a blood sinus with greatly swollen endothelium. The cells are of the characteristic Gaucher type, as described by Mandlebaum and Downey. They are large, circular, polygonal or irregular in form, with a wavy, wrinkled appearance, and contain irregularly shaped, colorless areas surrounded by the delicate wavy

fibrils within the cells. In many places the outlines of the cell body are obscured so that the cells appear fused into large plaques or syncytial masses. This is especially noteworthy in the hemorrhagic areas which practically consist of such masses affording a somewhat foamy appearance. The cells stain lightly with eosin. The nuclei are irregular in shape, eccentrically placed, small in comparison to the size of the cell body, and rich in chromatin network. There is abundant pigment, giving the iron reaction both in the unchanged parenchyma and in the Gaucher cells. The Malpighian bodies are small and unchanged.

There is no need to enter into a discussion of the pathology and pathogenesis of Gaucher's disease, for the last word has been said by the authors quoted above, to whose writings the reader is referred. Briefly summarized, Gaucher's disease represents a peculiar transformation of the reticulo-endothelial system involving the spleen, lymph nodes, bone marrow, and the Kupfer cells of the liver. The nature of this substance is not known, but Mandlebaum has shown that it is certainly not lipid; indeed, the substance is not extractable by any method at our command. This fact is important, because it enables us to differentiate Gaucher's disease from other conditions which resemble it histologically, notably certain cases of diabetes with lipoidemia, animals experimentally fed with a diet rich in fatty substance or cholesterin, and certain cases of cellular hyperplasia of the spleen due to tuberculosis.

Clinically, the history is quite atypical. The essential diagnostic features of this disease, the result largely of Dr. Brill's observations, who, by the way, was the first to diagnosticate the disease clinically, are these: The disease usually begins in childhood. There is a progressive enlargement of the spleen; also pigmentation of the skin of the exposed parts of the body, pin-gueculæ in the conjunctivæ, a tendency to hemorrhages (epistaxis or bleeding from the gums), and a leucopenia. The lymph nodes are not enlarged, and there is no jaundice nor ascites. There is excess of bile pigment in the urine and feces. The disease is marked by a pronounced chronicity so that years elapse before there is an appreciable increase in the size of the spleen. The disease is not directly fatal. It is sometimes fa-

milia, two or more members of the family being affected. Our patient was one of nine children. We have had the opportunity of examining only two others besides the patient. One had a large spleen, reaching a hand's breadth below the free border.

Discussion:

DR. WOOD: I should like to ask if any bone marrow was removed at the time the patient was operated on for the supposed osteomyelitis.

DR. MOSCHCOWITZ: No.

DR. KLEMPERER: Were there any changes in the blood picture of the child, that is, increase in the mononuclears? Is there anything known in regard to the peculiar changes in the skin? Also in regard to the lipid nature of the Gaucher cells, I would like to mention that Siegmund in a recent paper reported on a lipid cellular hyperplasia of the spleen in which he could find, on macro-chemical examination, phosphatides. He reported a case of a child two years old, and in the same family the mother and a sister had died of a swelling of the spleen and liver without a post-mortem examination. Siegmund concludes in his paper that possibly this case may be put between the lipid hyperplasia of the spleen in diabetic lipemia, experimental cholesterolemia on the one side, and the true Gaucher's disease in which no lipid is present on the other side. He thinks that the reticulo-endothelial cells may manufacture the lipid in some way. If I remember the paper right, it was the conclusion that the histochemical method confirmed the macro-chemical examination.

DR. MOSCHCOWITZ: I have the blood findings, and I do not recall that there was any increase in the mononuclears. As regards the skin lesion, I do not think that Mandlebaum mentioned anything about the changes in the skin.

HYALINE THROMBOSIS OF THE TERMINAL ARTERIOLES AND CAPILLARIES: A HITHERTO UNDESCRIBED DISEASE *

ELI MOSCHCOWITZ, M.D.

The history of this case is as follows:

A girl aged sixteen with an uneventful previous history and in a state of perfect health was suddenly attacked with a high fever (103° to 104° F.). The only complaint was pain in the arms. Even in the first days of her illness her physician noted an extreme pallor. She was admitted to Beth Israel Hospital a few days after the onset of the illness, where she remained one

* Presented January 10, 1924.

week, until her death. During her stay she ran a temperature between 101° and 102° F. There were a few petechiae on the arms. The hemoglobin was 40 per cent.; red blood cells 1,330,000; white blood cells 12,000, of which 65 per cent. were polymorphonuclears. The film showed many nucleated red cells. Her physical examination, aside from the above findings, was negative. Blood culture showed no growth. The urine showed some albumin and casts. Toward the end of her stay she had evidences of slight paralysis of the left arm and leg. She died in coma.

A partial autopsy showed the patient to be a poorly nourished, pale girl.

The lungs showed that both lower lobes were markedly congested; the remainder of the organs was pale.

The heart was slightly enlarged; the left ventricle was hypertrophied; the muscle was firm and pale. The mitral valve was normal; the aortic valve revealed nothing abnormal.

The liver was slightly enlarged, pale and fatty, and showed slight "nutmeg" change.

The spleen measured 11 x 8 x 3 cm., and weighed 165 gm. The surface was smooth. On section, it was a deep mahogany red, somewhat soft and velvety. The Malpighian bodies were prominent.

The kidneys were large; the capsule was smooth and not adherent. On section, they were deep red.

Anatomical Diagnosis: Anemia; acute congestion at bases of both lungs. Hypertrophy of the left ventricle. Hyperplasia of spleen. Congestion of liver and kidneys.

Microscopical examination showed the lungs to be edematous, but otherwise negative.

The heart muscle revealed a striking appearance. With the low power practically every field revealed from one to a dozen structures which are unquestionably thrombi in the terminal arterioles or capillaries. These vary in appearance and reveal progressive changes depending on the amount of organization that has taken place. The earliest show merely a plugging of the vessel with a hyaline mass which either partially or completely fills the lumen. Usually even in this stage the plug, if not in intimate contact with the wall of the vessel, is surrounded by a layer of flat cells of the fibroblastic type distinct from the endothelial intima. In older plugs, fibroblasts penetrate into the hyaline mass and the older the plug, the greater becomes the amount of fibroblastic infiltration at the expense of the hyaline material; eventually a small fibroblastic tubercle-like structure is formed. In some of these the origin of these fibroblasts from the endothelium of the vessel is plainly discernible. At the same time the process of organization within the lumen is accompanied by a fibroblastic process around the wall of the vessel in concentric fashion. With the Van Gieson stain some already give the reaction for fibrous tissue. Karyokinetic figures in these fibroblasts are common. In some vessels where the plug has not completely filled the lumen, tiny spaces are found in which fresh red cells are visible. Only the terminal arterioles

and capillaries are involved. The larger vessels with well-defined muscular walls show no change whatever, either in the form of thrombosis or changes in the intima. Every section of heart muscle is involved—the ventricles, auricles, the papillary muscles, and the septum. They are even visible in some of the vessels of the precordial fat. In addition, there is moderate edema of the parenchyma.

The liver shows a moderate fatty infiltration and slight congestion around the central veins. Very few hyaline thrombi in the early stage are noted.

The spleen shows marked congestion; the sinuses are enormously congested. There are a few hyaline thrombi in some of the central vessels of the Malpighian bodies.

The kidneys show marked parenchymatous degeneration in the tubules, and congestion. The Malpighian tufts are clear. Many of the arterioles and capillaries in the middle zone, in the region of the vasa recti, show hyaline thrombi of the same morphology as those in the heart. Stains for bacteria, tubercle bacilli, and the *Treponema pallidum* are negative.

A search of the literature reveals no similar case. Hyaline thrombi of the vessels have been known for many years; they occur isolated in the neighborhood of various lesions of infectious origin. They also occur in diseases of non-bacterial origin, such as eclampsia. But I have not been able to find any case in which they are so generally broadcast or in such a peculiar distribution. The nature of the hyaline thrombus is now generally known, as the result of Flexner's work, who demonstrated over twenty years ago that they were the result of the agglutination of red blood corpuscles. He was enabled to obtain such thrombi by the injection of the powerful agglutinizable substance, ricin. A year later, Pearce demonstrated that they could be produced by the injection of agglutinating sera.

The cause of the generalized thrombotic process in this patient remains a mystery. It apparently was due to a toxin with pronounced hemolytic and agglutinating property, and was apparently not bacterial.

Discussion:

DR. MACNEAL: Were there any foci of necrosis in the liver?

DR. MOSCHCOWITZ: The liver showed a little congestion around the central veins, and a few of the hyaline thrombi. There was no focal necrosis.

DR. MACNEAL: Was there any detective work done in regard to what the child had been eating in the country?

DR. JOBLING: I should like to ask if there was any possibility of the child having eaten poisonous mushrooms while she was in the country.

DR. MOSCHCOWITZ: That is possible, but we went very carefully into the history, and asked the parents about everything she had eaten, and there was nothing abnormal.

DR. MACNEAL: Was the question of mushrooms looked into?

DR. MOSCHCOWITZ: No.

DR. SEECOF: Had there been any injection of typhoid vaccine?

DR. MOSCHCOWITZ: No.

DR. MACNEAL: Did I understand the child had been away in the country? She might have gotten some wild mushrooms.

DR. MOSCHCOWITZ: She had been in New York for two weeks before the onset of her illness.

GUMMA OF THE MITRAL VALVE *

WILLIAM FRIEDMAN, M.D.

*(From the Pathological Laboratory of Mount Sinai Hospital,
New York City)*

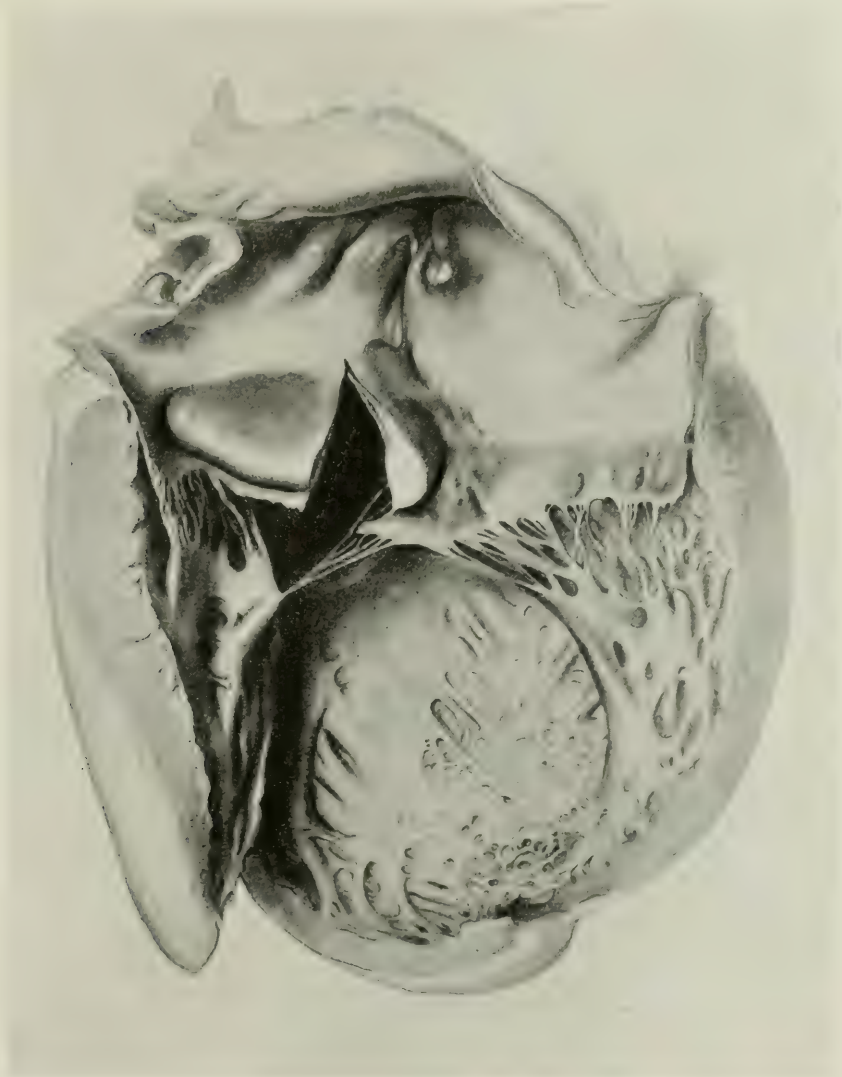
A luetic lesion of a heart valve is very rare, the usual involvement of the valve being due to an extension of the process from the adjacent myocardium. When the lesion is confined to the valves the aortic cusps are those most often involved. A type of verrucous endocarditis has been described in cases of lues, but this is probably a coincidental endocarditis. The gummatous type which corresponds to the case now reported is extremely uncommon.

The patient, a male, 40 years old, was admitted to Mount Sinai Hospital, on July 17, 1923, with the history of pain in the precordium radiating to the shoulders, and severe cough for two months. This was accompanied by a thick, greenish expectoration. Two weeks prior to admission he had attacks of extreme dyspnea and constant pain in both lower extremities. The patient denied having had any venereal disease, but complained of frequent sore throat.

On admission he appeared acutely ill and markedly dyspneic. There was slight icterus of both scleræ. The eyes reacted to light and accommodation. The heart was normal in size, but a systolic murmur was heard at the apex which was transmitted into the axilla. The pulses were Corrigan in type and a pistol-shot sound was heard over both femoral arteries. The lungs showed an area of dullness over the entire right chest, anteriorly and

* Presented February 14, 1924.

posteriorly, and numerous moist râles were present at both bases. The liver was enlarged and tender, the lower border reaching to the level of the umbilicus in the midline. The temperature on admission was 100.2° F.; pulse 84; respirations 26. The temperature gradually rose for one week reaching 105.4° on the day of his death. The blood pressure was systolic 140; diastolic 49. The blood count showed a slight leucocytosis; the sputum was negative for tubercle bacilli; the blood Wassermann was 4 +, and the urine showed a moderate amount of albumin. The jaundice gradually increased in intensity.



Drawing of heart opened to show a gumma of the mitral valve

In describing the autopsy findings only the relevant details will be given. The heart was enlarged, weighing 700 gm. The musculature was salmon-pink in color. There were no gross areas of scarring in the myocardium.

The right side of the heart was moderately dilated, the left side considerably hypertrophied. The tricuspid and pulmonary valves were negative, but the entire mitral valve was thickened. In the aortic cusp of the mitral valve there was a rounded, hard mass which penetrated the entire thickness of the cusp and measured 3.5 cm. in diameter and from 0.75 to 1.25 cm. in thickness (Fig. 1). On section, it was found to be deep yellow in color and hard in consistency. There were several smaller, lighter areas in the mass which were softer than the surrounding tissue. The process extended upward slightly upon the endocardium of the left auricle. The musculature of the left auricle was not involved in the process. The aortic valve was thickened along its entire edge. The wall of the arch of the aorta was greatly thickened, apparently due to an increase in the width of the media. The intima was deeply scarred and wrinkled. The ascending portion of the arch was distinctly dilated. The rest of the thoracic and abdominal aorta showed marked scarring throughout. In the lungs there were numerous recent areas of infarction with organizing thrombi in the vessels corresponding to these areas. The liver weighed 1,300 gm. It felt rather soft and the capsule was smooth. The cut section was deep yellow in color and showed what appeared to be a degeneration of the central portions of the lobules.

The microscopic sections of the mass in the mitral valve showed areas of diffuse round cell infiltration, the central portions of which were necrotic. There were no giant cells present. There were also areas of dense connective tissue with the formation of capillaries. Sections of the aorta showed marked thickening of the intima and scarring of the media, with perivascular round cell infiltration and newly-formed blood vessels. The adventitia also showed marked round cell infiltration. Levaditi stains on sections of the mass in the mitral valve and the aorta revealed no spirochetæ. This was probably due to the fact that there had been an agonal gas bacillus invasion of all the tissues of the body. The microscopic examination of the heart muscle showed numerous small areas of degeneration of muscle fibers and marked perivascular fibrosis. The sections of the liver revealed a diffuse necrosis of the central two-thirds of the lobules.

Notwithstanding the absence of spirochetæ in the lesions of the mitral valve, for the reason given above, the histological appearance, in conjunction with the typical luetic aortitis and the positive complement fixation, justifies the diagnosis of a gumma of the mitral valve.

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TUBERCULOMA OF THE CECUM *

LEO EDELMAN, M.D.

(From the Pathological Laboratory of Mount Sinai Hospital, New York)

The interest in ileo-cecal tuberculosis, particularly the hypertrophic form or tuberculoma, began in 1891, when Hartmann¹ and Pilliet in Paris, and Billroth in Vienna, simultaneously described the condition as tuberculous typhlitis frequently mistaken for a malignant neoplasm.

I am presenting this specimen of tuberculoma of the cecum, because of its comparatively infrequent occurrence, together with the fact that it illustrates how easily it might have been taken for a malignant tumor without the aid of microscopic examination.

The patient, from whom this specimen was removed, a male, age 35, was operated upon by Dr. Albert A. Berg, March, 1923, because of abdominal pain and the presence of a tender mass in the right lower abdomen. His appendix had been removed by another surgeon at some prior date. Only a meager history was obtainable.

At operation a mass about the size of an orange was found involving the cecum and densely adherent to the neighboring tissues. The diseased cecum, including ascending colon, and about six inches of terminal ileum were removed, the ends of the ileum and colon closed, and a side to side ileocolostomy performed.

The patient had an uneventful convalescence and left the hospital five weeks after operation in excellent condition. He has gained weight and is feeling perfectly well at the present time.

The specimen (Fig. 1) received by Dr. F. S. Mandlebaum for examination consists of the cecum, ascending colon and 16 cm. of the ileum. The cecum and ascending colon measure 22 cm. in length (after hardening). The ileum, except for a moderate thickening of its wall, is quite normal. The cecum is represented by a firm nodular mass partly covered by a densely adherent fibro-fatty sheath of mesenteric fat and adherent omentum. The enlargement is somewhat oval in shape and extends upwards involving approximately half of the resected ascending colon. Several firm glands are present in the mesenteric fat in the region of the ileo-cecal angle. Longitudinal section reveals extreme thickening of the walls of the cecum and ascending colon for a distance of 12 cm. from the caput. It ends rather abruptly as a constricting ring with ulceration of the mucosa. The lumen is contracted, irregular in caliber, varying between 10 and 20 mm. The ileo-

* Presented February 14, 1924.

cecal opening is likewise constricted but there is no apparent involvement of the ileum. The mucosa in the diseased area appears roughened, is hemorrhagic, and shows an occasional polypoid projection and in places is ulceronecrotic covered with a grayish exudate. The wall is firm, dense, pearly gray in color, hemorrhagic near the mucous surface and varies in thickness between 3 and 20 mm., the greatest thickening being in the region of the ileo-cecal junction.

The lymph nodes are small, 5 to 10 mm. in diameter, and on section are firm, pinkish in color, strongly suggestive of new growth. There is no evidence of caseation.

The microscopic sections show that the entire thickness of the wall is involved by the disease process. The surface epithelium appears atrophic, in

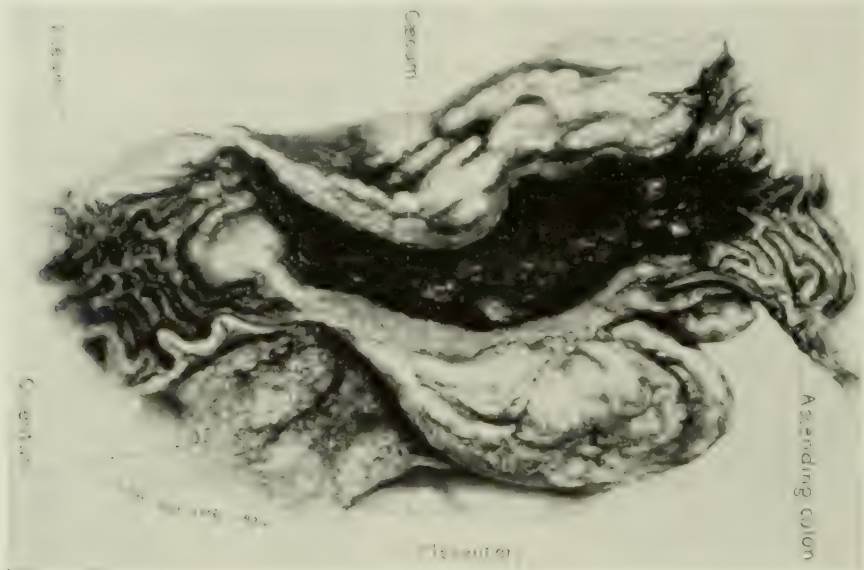


FIG. 1. Tuberculoma of cecum.

places almost completely destroyed and replaced by round cell infiltration containing giant-cells. The submucosa appears hemorrhagic, diffusely infiltrated with typical tubercular granulation tissue and tubercles containing giant-cells (Fig. 2). The same process extends down to the serosa causing interruptions in the continuity of the muscularis with replacement by new-formed cellular and dense fibrous connective tissue surrounding groups of epithelioid cells containing giant-cells. The mesenteric lymph nodes present numerous typical tubercles with giant-cells surrounded by dense fibrous connective tissue showing no tendency to caseation. Tubercle bacilli are present in the tissue sections.

The report submitted by Dr. Mandlebaum was tuberculoma of the cecum and ascending colon.

The hypertrophic form of tuberculosis nearly always com-

mences in the cecum or the ileo-cecal angle and runs a chronic course. It appears to be equally common in both sexes, and though usually found between the ages of twenty and forty, may occur at any age. Billroth refers to a case in a child of ten. Gage and Hunt⁶ report one in a man of seventy-one.

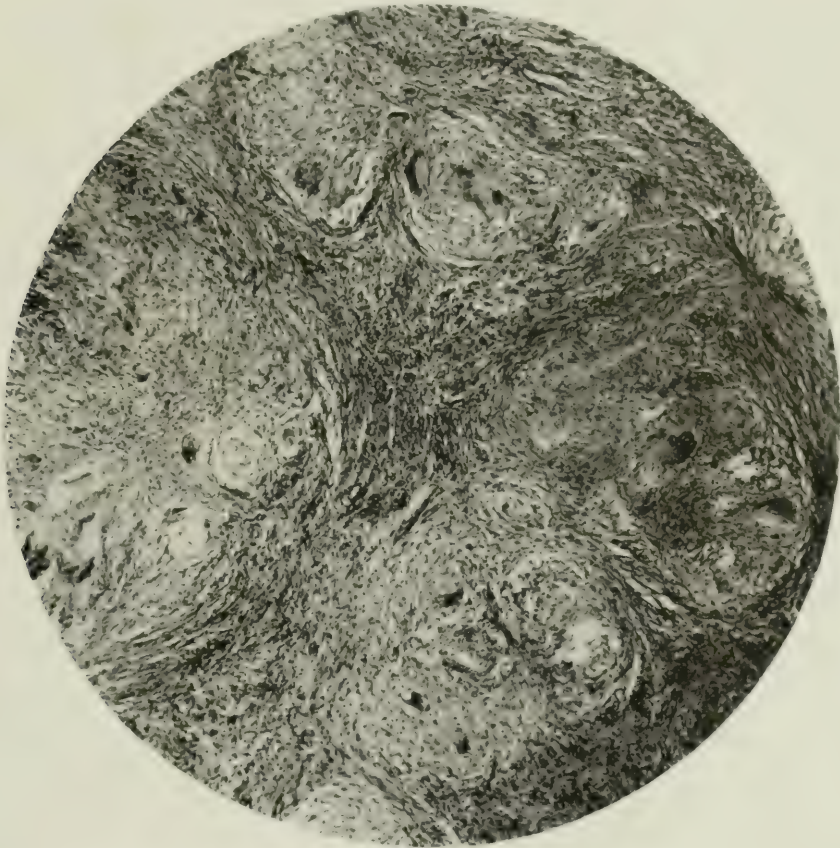


FIG. 2. Photomicrograph of lesion showing typical tubercles containing giant cells. Low power.

The pathologic process seems to be a tubercular invasion by way of the mucous membrane, according to Hartmann,² Baum³ and others, often primary, commencing in the cecum, close to the ileo-cecal valve. The lesions are most pronounced in this region and for that reason Dieulafoy⁴ applied the term "hypertrophic tuberculoma of the cecum." The tuberculoma may remain limited to the cecum without invading the colon. In most of the published cases, however, it spreads along the intestine reaching

the ascending or transverse colon. This indicates the necessity for wide resection.

The only treatment for this form of tuberculosis is surgical. It is necessary to operate as early as possible, before the patient is cachectic, and as soon as the disease is diagnosed or even suspected. Hartmann² advises ileo-colostomy with resection. In summarizing the results of operations reported in the literature, he records thirty-one cases of resection with side to side anastomosis, with twenty-six recoveries and five deaths, and twenty-nine cases of ileo-colostomy with twenty-five recoveries and four deaths.

Most of the cases reported in the literature since 1891 are by foreign observers. Wiener,⁵ in 1914, appears to be the first surgeon to have reported a series of cases in this country.

In closing, I wish to express my indebtedness to Dr. Berg and Dr. Mandlebaum for the clinical data and the privilege of presenting the pathological specimen.

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Discussion:

DR. ASCHNER: We are apt to think that tuberculous infection of the bowel occurs by way of the lumen of the bowel, and spreads along the mucosa. In looking up the question of congenital cysts of the intestine, I found a case in which there was an enterocyst of the intestine entirely separate from the lumen of the bowel. The intestine in this case was affected by tuberculosis, and the lining of the cyst, which was similar to that of the intestine, was of mucous membrane which showed the same tuberculous lesion as the rest of the bowel did. That is an observation suggesting that infection occurs through the blood stream, and not by way of the surface mucosa.

DR. WOOD: It is certainly true, as Dr. Edelman said, that these lesions are easily mistaken for neoplasms. In many instances they have been so considered by the surgeons.

PERIRENAL ANGIOSARCOMA *

PAUL W. ASCHNER, M.D.

Neoplasms arising from the renal capsule, the perirenal fat or the perirenal fascia are of relatively infrequent occurrence, tumors of the kidney being fifty times as common. They offer, however, interesting problems in diagnosis and treatment when encountered.

The first specimen is one removed by Dr. S. Wiener in October, 1919. A married woman, thirty-seven years old, had noticed undue prominence of the right side of the abdomen for about a year. A sudden attack of pain in this region accompanied by chilliness and vomiting brought her to the hospital. She appeared to have lost weight. A mass presented in the right flank, extending almost to the mid line and down to the level of the anterior superior spine of the ilium. It was firm but elastic, slightly movable, not tender. Vaginal examination was negative. The urine showed no changes. Cystoscopy showed diminished function of the right kidney, but pyelography showed normal pelvis and calyces. At operation the tumor was found to be retroperitoneal, and encapsulated. The upper part was solid but friable; the lower part was hemorrhagic. In the process of isolating the tumor it was found so intimately connected with the structures of the kidney hilum as to necessitate removal of that organ.

The tumor measured about 10 cm. in diameter. On section it showed an outer white cellular zone, and an inner yellowish degenerated and somewhat hemorrhagic zone. It seemed to arise from the loose cellular tissue about the hilum of the kidney. The latter organ and its tunica were uninvolved by the growth, although tumor tissue was adherent to the kidney capsule and pelvis in the region of the hilum. The suprarenal gland was not removed.

Microscopic examination of various sections of the tumor showed it to be made up of loose connective tissue and fat, numerous blood vessels the size of small arterioles, and extending from the outer limits of these vessels polymorphous cells arranged in palisade formation. These cells had large nuclei with prominent nucleoli. In some areas solid masses of them invaded the perirenal areolar and fatty tissue. The arrangement was that described as perithelial sarcoma or perithelioma. The large number of blood vessels led us to classify the tumor as an angiosarcoma.

It is of interest that this patient has remained well four years and has regained her normal health and weight. She was recently presented by Dr. Wiener without any subjective or objective symptoms of recurrence. X-ray of the chest showed no abnormality at this time.

The second specimen was removed by Dr. H. Neuhof in December, 1922.

* Presented February 14, 1924.

A woman twenty-seven years of age had complained of fulness after meals for only a few weeks. On the day before she entered the hospital she was seized with sudden severe pain in the right flank and right side of the abdomen increasing in severity. She vomited several times but the bowels responded to an enema. There were chilly sensations all day and when examined at the hospital she had a definite chill and was in a condition of shock. A smooth cystic mass was palpable in the right upper quadrant of the abdomen. It was about 13 cm. in diameter, and very tender. The muscles of the parietes were rigid over it, and there was peritoneal rebound tenderness.

At operation the tumor was found to be retroperitoneal and purplish in color due to hemorrhage. It was encapsulated and in the process of removal was seen to be adherent to the upper pole of the right kidney. A small portion of the latter was excised with the main mass. The specimen on section presented a diffuse hemorrhagic infiltration, areas of pure blood clot intervening between areas of yellowish friable tumor tissue. The portion of kidney parenchyma received with the specimen appeared uninvolved, but the tumor was intimately adherent to the renal capsule. On microscopic section this part of the renal capsule was found composed of vascular spindle celled sarcoma. The rest of the tumor was vascular and infiltrated with blood. About the vessels were nests of sarcoma cells chiefly of the spindle form. The nuclei were not large and mitotic figures were absent.

The possible origin of the tumor from the suprarenal gland was suggested by one section of the tumor. Here cuboidal and polygonal cells with clear protoplasm were arranged in irregular strands between fine capillaries. But as these cells could be regarded as embryonal fat cells, and as the rest of the tumor did not present confirmatory evidence, the diagnosis of perirenal angiosarcoma seemed the more reasonable. It did not conform to the descriptions of adrenal tumors presented by Winkler.

The patient was re-examined a year later. She showed no signs of recurrence and had gained thirty pounds in weight.

The most comprehensive review of the subject of perirenal tumors is that presented by M. P. Lecène (*Association Francaise de Chirurgie*, 1919, xxviii, 533). He collected 113 proved cases, comprising many varieties of benign and malignant neoplasms of mesoblastic origin. Among them were only two angiosarcomas.

Discussion:

DR. WOOD: I think the interest of these sections and those of the perirenal angiosarcoma is sufficient to warrant their being referred to the Committee on Microscopy for a written report. It is interesting to have the opinion of two or three other men, and their report ought to be embodied in the record of these cases. Our surgical colleagues labor under great disad-

vantage as compared to us in the case of demonstration of material, and they are apt to be very critical in that there are certain differences in nomenclature, and object to the fact that some men class a tumor as an osteogenic sarcoma, and some others call it an osteo-chondro-sarcoma. That is regarded as a terrible defect in pathology. Because all of us pathologists do not agree on the nomenclature, complex tumors of this sort ought to be seen and discussed. We recently had a similar case at St. Luke's Hospital in which a diagnosis of myoma of the stomach wall was made. The tumor recurred with fair promptness, and it is now a pure sarcomatous type. The early sections are still fibromyoma under the microscope, and the later sections could be diagnosed by any medical student. What has been the change and why, are things we cannot explain at the present time. It is important, I think, that these rare types of tumors be studied in greater detail, under good conditions, and that a written report be made upon them.*

LEIOMYOMA AND LEIOMYOSARCOMA OF THE GASTROINTESTINAL TRACT †

FREDERIC D. ZEMAN, M.D.‡

(From the Pathological Laboratory, Mount Sinai Hospital, New York)

Tumors composed of, or arising from, smooth muscle may be sharply differentiated from other mesodermal neoplasms of the gastrointestinal tract. In the past three years we have had the opportunity to study four such tumors of the benign type and three of the malignant variety. One of the latter group was a mixed tumor, presenting features of unusual interest.

LEIOMYOMA

The benign smooth muscle cell tumors occur in all parts of the gastrointestinal tract, and may take their origin from the

* At Dr. Wood's request, the slides were referred to the Committee on Microscopy, and the report of Dr. Ewing follows.

DR. EWING: The tumor appears to arise in the fat tissue. It consists in a marked overgrowth of small and medium sized arterioles, around which the fat cells, and possibly the perithelial cells, are proliferating considerably. In places the proliferation of fat cells seems to be diffuse. Histologically it may be called an arterial angioma or angiosarcoma, but most of the tumor cells seem to be derived from fat cells. Its malignancy must be doubted. The two tumors are essentially the same.

† Presented on February 14, 1924.

‡ Work done under tenure of Moses Heineman Fellowship in Pathology.

muscularis mucosæ, the circular, or longitudinal muscle layers. Those arising from either of the two inner layers tend to project into the lumen of the gut, and may become pedunculated and polypoid in appearance. Those originating in the outer longitudinal layer of the muscle become subserous, and tend to reach a larger size than the internal variety. Such tumors arising from the greater curvature of the stomach, and attaining a weight of 2.5 to 5.5 kilos, have been successfully removed by surgeons (v. Eiselsberg,¹ Erlach,² Kaufmann³). Occasionally the internal type may undergo ulceration and profuse hemorrhage result. Again, such tumors when pedunculated have been known to cause pyloric obstruction (Lotsch⁴). As a general rule, however, the tumors are small, frequently multiple, and found only accidentally in the course of careful operative exploration, or post-mortem examination.

Grossly they appear as small, firm, elastic nodules raising up either serosa or mucosa, which is usually thinned out and atrophic. On cut section, they are yellowish-white in color, surrounded by a definite capsule, which extends through the tumor as lighter colored intersecting strands. Microscopically one notes a characteristic pattern of intertwining muscle bundles cut both longitudinally and transversely. The amount of connective tissue varies greatly in different tumors, even from the same subject. The cells stand out prominently from one another, and are elongated with long slender nuclei having rounded ends. Due to the acidophile cytoplasm, striking and instructive microscopic pictures are obtained with the Van Gieson stain, which serves on occasion to differentiate other types of neoplasm. Degenerative changes such as cyst formation, hyalinization and calcification are not uncommon. Cases have been described in which small islands of glandular epithelium were found in the midst of myomatous tissue in the stomach. These adenomyomas have been interpreted as arising from misplaced pancreatic rests (Trappe,⁵ Cohen⁶).

CASE I. S. S., male, age forty-nine, was admitted with signs of acute appendicitis and peritonitis. Six days after operation, he succumbed to a bilateral purulent broncho-pneumonia. Post-mortem examination revealed,

in addition to the other findings, a firm, elongated nodule in the esophagus, 2 cm. in length and 3 mm. in width, about 1 cm. above the bifurcation of the trachea. The mass lay obliquely to the long axis of the esophagus. On cut section, it was firm and grayish-white in color. Microscopic examination showed typical leiomyoma with areas of calcification in the center.

CASE 2. M. B., female, age sixty-five, developed empyema thoracis, following pneumonia. Three days after operation the patient died. In the course of the autopsy two small, firm nodules, irregularly oval, measuring 5 mm. and 11 mm. in diameter, were encountered beneath the mucosa of the fundus of the stomach. Microscopic examination showed typical leiomyoma, although in the smaller tumor fibrous connective tissue formed about one-third of the mass.

CASE 3. J. H., male, age fifty-nine, suffered from a squamous-celled carcinoma of the esophagus, causing marked stenosis. While performing a gastrostomy the surgeon observed a small, ovoid nodule about 8 mm. in the long axis, well circumscribed, beneath the serosa of the pyloric portion of the stomach. This nodule he resected. Under the microscope it was found to consist of smooth muscle.

CASE 4. E. L., female, age twenty-five, was admitted with symptoms of chronic appendicitis. In course of abdominal exploration, the operator felt a small mass on the posterior wall of the stomach near the lesser curvature. This was found on removal to be a submucous pedunculated tumor, about 1.5 cm. in diameter. Microscopically, the diagnosis was leiomyoma. The patient made an uneventful recovery.

LEIOMYOSARCOMA

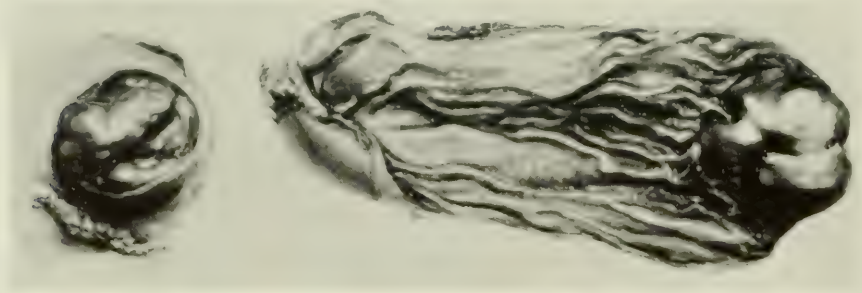
The foregoing cases have been described partly because of their intrinsic value, but chiefly with regard to their importance in the pathogenesis of malignant tumors of similar and related types. The question of sarcomatous degeneration of myomata, especially in the uterus, is one that has long vexed pathologists, but at present the tendency is definitely in favor of the recognition of this change. Anshütz and Konjetzny⁷ cite two cases of their own, and numerous instances from the literature where this transition has been traced with great certainty. These authors feel that myomata of the stomach may give rise not only to myosarcomata, but also to fibro-, myxo-, and spindle-celled sarcomata.

Like the myomata, the myosarcomata of the gastro-intestinal tract may be either internal or external in location, sessile or pedunculated, and not infrequently attain great size. In general

they are rapidly growing, extremely invasive tumors, metastasizing in mesenteric and retroperitoneal lymph nodes and the liver most frequently, but only rarely above the diaphragm.

Microscopically they are extremely cellular with relatively little stroma. The cells are spindle-shaped, the nuclei are elongated with rounded ends, rich in chromatin, staining deeply with hematoxylin. Giant cells with bizarre nuclei are not uncommon. Mitoses are frequent. The blood supply is usually abundant. With the Van Gieson stain the acidophile character of the cytoplasm may be brought out in characteristic fashion.

CASE 5. L. W., female, aged forty-one, complained of weakness and melena over a period of two years. Three years before admission a benign tumor causing metrorrhagia necessitated supra-vaginal hysterectomy. Roentgen examination with barium meal revealed a circular defect about 2.5 cm.



Stomach of Case 5, showing sharply circumscribed globular tumor. At the left the peritoneal surface of the tumor is shown with the serosa dissected off.

in diameter in the body of the stomach near the greater curvature. Within the defect, almost at the center, was noted a persistent patch of barium, which was interpreted as a crater. On the basis of these findings a gastric neoplasm, possibly benign, was diagnosed. At operation, a tumor about 5 cm. in diameter was found involving the antral portion of the stomach on the greater curvature, apparently involving all coats of the stomach and projecting into the lumen of the stomach. The tumor was yellowish-white in color, moderately firm in consistency, and grossly appeared to be sharply circumscribed and encapsulated. Microscopically, a richly cellular tumor was found, which in places was suggestive of leiomyoma, but in others presented signs of active cellular proliferation and extension of neoplastic cells into the tissues outside of the capsule. The picture was that of a leiomyoma which had undergone sarcomatous change.

CASE 6. A. M., aged sixty-three, had suffered from anorexia for six months. For the past two months before admission he had noted abdominal

cramps, watery stools, loss of weight and an abdominal mass. Examination revealed moderate abdominal distention, enlarged liver, visible peristalsis and a large, irregular, hard mass in the hypogastrium and the left lower quadrant. About eight days after hospitalization, the patient suffered an attack of acute abdominal pain associated with vomiting and tachycardia. Signs of diffuse peritonitis were present. Operation revealed a diffuse purulent peritonitis. The coils of small intestine were thickened and infiltrated by tumor tissue, giving to the palpating finger the sensation of a length of rubber hose. Several days later the patient died.

At post-mortem examination a diffuse purulent peritonitis was found. Adhering to the edges of the wound was a large, irregular, cauliflower-like mass of soft, friable, tumor tissue, which seemed to arise in the mesentery of the small intestine. The stomach wall was somewhat thickened, as were also the duodenum and first three feet of jejunum. About 2.5 meters from the pylorus loops of jejunum for a distance of 80 cm. were matted together in a mass of tumor tissue. On opening this portion of the intestine numerous tumor masses were found, varying in size from 0.5 to 4 cm. in diameter. At the site of the largest mass the lumen was considerably narrowed. On cut section, these masses appeared to be growing through the thickness of the gut wall into the mesentery and involving the mesenteric nodes. They were light yellow on section, friable and hemorrhagic in places. Near the mesenteric attachment in this portion of the jejunum involved by tumor, was found an irregular perforation, undoubtedly the origin of the peritoneal infection.

Sections of this tumor showed an actively growing invasive tissue, consisting of polymorphous cells, chiefly spindle-shaped, with elongated deeply staining nuclei. Numerous mitoses were noted. Here and there giant cells with pycnotic irregular-shaped nuclei were noted. Sections of other organs showed no involvement by tumor.

CASE 7. H. S., male, aged fifty-five, had noticed increasing weakness and dyspnea for several months. Six weeks before admission epigastric pain, heart burn, and tarry stools had been noted with slight loss of weight. Physical examination showed marked secondary anemia, abdominal distention with tenderness in epigastrium and right upper quadrant, and enlargement of spleen. Gastric contents contained no free hydrochloric acid; blood, lactic acid and Boas-Oppler bacilli were present. Roentgen examination of the stomach presented changes interpreted as indicating the presence of a perforating gastric ulcer on the posterior wall which formed an accessory pocket in the adjacent organs surrounded by dense adhesions. Due to the extensive nature of the lesion a malignant tumor was considered very probable.

Following a transfusion of citrated blood operative interference was undertaken. Almost the entire middle third of the stomach was found to be involved in a huge tumor mass, mostly on the greater curvature and attached to the transverse colon. The mass was the size of a baseball. The regional lymph nodes were greatly enlarged and hard. The pancreas was not involved. The stomach and transverse colon were resected; gastro-jejunosomy and colonic anastomosis were performed.

Examination of the specimen showed a large ulcer on the greater curvature of the stomach with thick heaped-up edges, in the center of which was a perforation toward, but not into, the transverse colon. The tissues around this defect were densely infiltrated by firm, grayish-white, neoplastic tissue.

Microscopic examination showed an unexpected condition. Beneath the intact gastric mucosa were densely packed polyhedral and spheroidal cells with round deeply staining nuclei, which were apparently epithelial in origin, but definitely not adenocarcinomatous. Toward the depths of the stomach wall and in the walls of the colon, the cells were spindle-shaped, with elongated nuclei arranged in parallel strands, actively invasive and showing numerous mitotic figures.

At the autopsy table the liver was found to be extensively involved by numerous small, hard, white nodules, and by a large cystic mass in the upper part of the right lobe. Microscopically these tumors consisted entirely of sarcomatous tissue. On the upper surface of the pancreas and near the ileocecal junction were noted implantation nodules of similar appearance, both grossly and microscopically.

In this case we are dealing probably with a mixed carcinoma and sarcoma, with marked predominance of the latter elements, as is usually the finding in this type of tumor (Anschütz and Konjetzny⁸).

Each one of these last three cases may be considered as illustrating an important phase in the natural history of leiomyosarcoma. The first represents the development of malignant change in a benign muscle cell tumor. The second is an example of the end-stage of this highly invasive neoplasm; while the third illustrates the response of both mesodermal and endodermal elements to whatever agent may be the inciting cause of autonomous cell growth.

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FOLLICULOID CARCINOMA OF THE OVARY *

M. A. GOLDBERGER, M.D.

(From the Pathological Laboratory, Mount Sinai Hospital, New York City)

The specimen I am presenting is a rather rare type of ovarian tumor. It was removed in the course of an operation for multiple fibroids of the uterus on October 23, 1923, by Dr. J. Brettauer. The history briefly is as follows:

The patient, Mrs. E. F., was forty-nine years old. Her menstrual periods were irregular and scant. She had three living children, the youngest being twelve years old. The patient was under observation by her doctor for three years who noticed a gradual enlargement of the uterus. It was irregular, hard, the size of a three months' gravidity and was wedged into the pelvis. She complained of pain in both thighs and inability to do much walking.



Drawing of tube and ovary with folliculoid carcinoma replacing most of ovary

Casual inspection of the ovary in which this tumor was situated gave one the impression that it contained an hemorrhagic cyst. On section its ap-

* Presented February 14, 1924.

pearance is rather striking. The tumor, measuring 5 cm. in diameter, replaces the major portion of the ovary. Its bulk is made up of an hemorrhagic cystic mass and a small yellowish-white, semilunar area situated on its upper outer edge about 1.5 cm. long and 0.75 cm. wide.

Histologically this tumor is composed of epithelial masses in an unchanged ovarian stroma. These masses vary in size and shape, their cells being rather large, polygonal in shape, and containing central oval nuclei that are rich in chromatin. Some are mitotic. Most of these cell masses contain areas in which the cells group themselves into areolar forms like the spokes of a wheel and in their center there are several cells undergoing degeneration. It is these areas that give these tumors their distinctive peculiarity. In the hemorrhagic portion of the tumor the cell masses contain cysts. These cysts vary in size and in the thickness of their limiting wall.

This type of tumor has given rise to much discussion and speculation as to its histogenesis. Goodal has shown that all embryonic remains in the ovary, including the medullary cord and rete cells, are downgrowths of the original germinal epithelium. In other words, no matter from what part of the ovary epithelial growths arise, they all originate from the germinal epithelium. In view of our experiences in oncology it is unlikely that the source of origin of these tumors is the follicular epithelium. This tumor most likely arises from the medullary cord or rete cells or their forerunner, the germinal cells, which are practically the only ones capable of mimicing the ovarian follicle. Goodal calls this a "pseudo-oogenic process." Geist reported a similar tumor and mentioned the tendency to cyst formation in these growths. He suggested that the origin of ovarian cysts may possibly be explained in this manner. In my specimen cyst formation also seems to be a striking feature. The presence of mitotic figures, which are rarely found in these tumors, together with a tendency for infiltration of the surrounding stroma, places this neoplasm in the class of malignant tumors. In the gross as well as morphologically, the tumor described by Geist resembles the specimen presented except for the differences mentioned. It is this tumor that I think is correctly termed folliculoid carcinoma, and the terms adenoma of the Graafian follicle, oophoroma folliculare or folliculoma should be reserved for the type described by Geist and others.

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KIDNEY CHANGES IN PYLORIC OBSTRUCTION *

F. D. ZEMAN, WILLIAM FRIEDMAN AND L. T. MANN

(From the Pathological Laboratory, Mount Sinai Hospital, New York City)

Four cases of pyloric obstruction have been studied with particular reference to the microscopic changes in the kidney. Of the four, two showed clinically typical tetany, presumably of gastric origin. One of these was under observation only twenty-four hours, and was unoperated, dying shortly after admission to the hospital. The other case, in which a huge gastrectasia was demonstrated by Roentgen-ray, developed tetany following operative resection of the stomach. The two cases without tetany both had symptoms of gastric ulcer with signs of obstruction, and were treated surgically.

The kidney changes were not appreciated before death, and were only discovered in the course of routine microscopical examination of autopsy material. The four cases show almost identical kidney changes. These consist in degeneration of cells lining the spiral and terminal straight portions of the first convoluted tubules. In many sections these cells are necrotic and infiltrated by granules staining dark blue with hematoxylin, which merge into larger masses, entirely blocking the lumina of the tubules. These blue-staining granules we have interpreted as calcium salts whose staining reaction with hematoxylin is generally regarded as highly characteristic. Treatment of sections with 5 per cent. nitric acid for twenty to thirty minutes and the staining with hematoxylin showed complete disappearance of blue-staining material. Van Kossa's silver nitrate stain likewise showed these deposits to be composed of calcium.

* Presented February 14, 1924.

The changes we have found in these kidneys have long been regarded as a frequent concomitant or result of poisoning with mercuric chloride. The similarity is so marked that in our first case we were for a time entirely misled. It must be emphasized that we do not consider these kidney changes as evidences of a true nephritis. The cardinal signs and criteria of either an acute or chronic inflammatory lesion are entirely lacking. The changes we have observed are entirely of a degenerative nature, and as such are best designated by the term toxic degenerative nephrosis.



FIG. 1. Photomicrograph of human kidney, showing degeneration and calcification of convoluted tubules. Low power

The observation that gastric tetany may be accompanied by renal changes was first made by Nazzari, who in *Policlinico*, 1904, reported two cases of gastric tetany with calcification of renal convoluted tubules. He had observed a similar picture in cases of mushroom poisoning and held that his findings pointed to the toxic origin of tetany.

This work remained without confirmation until very recently when a group of workers from the Mayo Clinic, Brown, Hartman, Eusterman and Rowntree¹ reported eleven cases of duodenal toxemia resulting from high intestinal obstruction in which they found renal changes, which they described as either a dif-

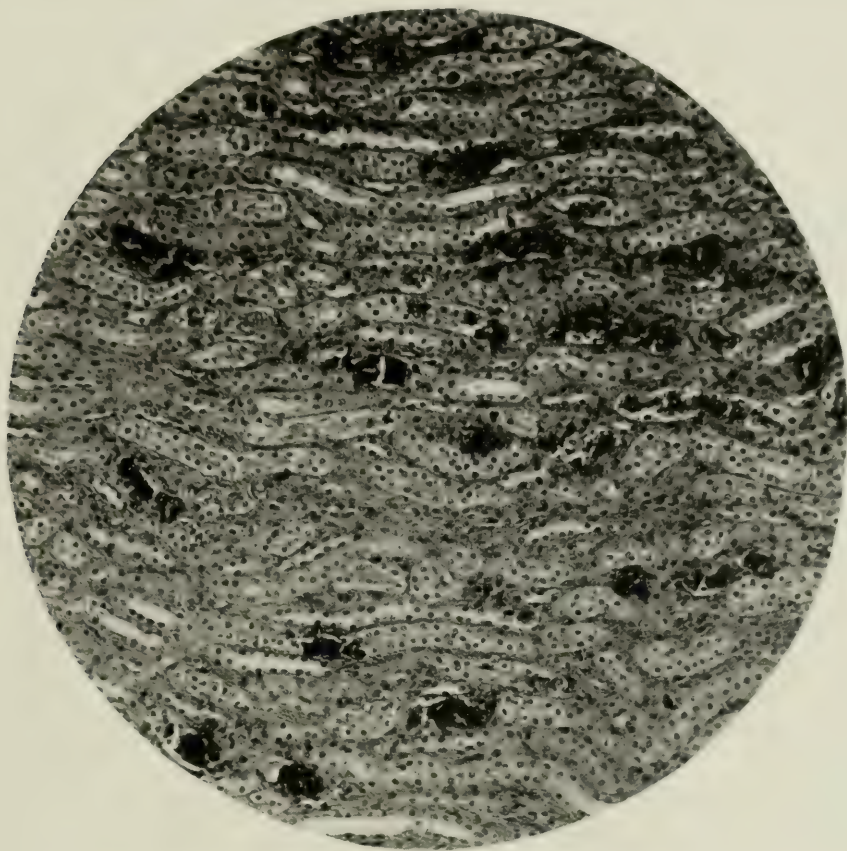


FIG. 2. Photomicrograph of cat kidney, showing experimentally produced degeneration and calcification of convoluted tubules. Low power

fuse nephritis or a nephrosis. Calcification occurred in several of their cases, but they attribute this to administration of calcium by mouth. While their work is complete, with full chemical and clinical observations, we cannot as yet subscribe to their interpretation of the findings which are in general similar to our own. Notwithstanding the fact that three of our four cases received calcium internally, we do not feel that this has any direct bearing on the character of the kidney lesions described.

We feel that the primary factor in our observations is pyloric

or high duodenal obstruction in association with repeated vomiting, to which the tetany and kidney changes appear to be secondary. The mechanism leading to the kidney damage we are unable to explain satisfactorily. Sections of stomach and other organs in our series showed no deposit of calcium, such as occurs in metastatic calcification, where the amount of circulating calcium is increased.

The clinical observations are being tested in the experimental studies which we are now undertaking. By tying off the pylorus of cats, it has been possible to reproduce experimentally kidney lesions similar to those described in human beings.

In thirteen cats so operated upon, and sustained by subcutaneous injections of 10 per cent. glucose solution thrice daily, we have found kidney changes in eleven. The earliest changes, consisting of necrosis with beginning calcification, have been noted within forty-eight hours after operation. Due to the difficulty of interpreting tubular degeneration, we have only considered positive those kidneys showing definite calcification.

Grossly, the kidneys show marked cloudy swelling and congestion, especially in the pyramids, which have a characteristic violaceous tint, described by some observers in human kidneys poisoned by mercuric chloride. Microscopically, there is diffuse tubular degeneration, with necrosis and calcification occurring first in the spiral and the terminal straight part of the convoluted tubules, and later in the portions of tubules adjacent to the glomeruli.

The chemical findings in the experimental animals confirm those of Hastings, Murray and Murray,² Middleton and Murray,³ Haden and Orr,⁴ Wilson, Janney, and Stearns⁵ and McCann.⁶ They show a rise in CO₂-combining power of the plasma with a drop in the plasma chlorides, as well as an increase in the non-protein nitrogenous constituents of the blood. The calcium in the blood serum shows either no change or changes too slight to admit of interpretation.

The pathological changes in the kidneys may very well account for the nitrogen retention, but to what the kidney damage may be attributed we are at present unable to determine.

In our further studies we intend investigating (1) renal function; (2) whether the injection of acid solutions will prevent the occurrence of kidney changes, and (3) whether the process is a reversible one, that is, whether releasing the ligature around the pylorus will bring about a restoration of normal conditions in the blood and in the kidneys.

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Discussion:

DR. BAEHR: I should like to emphasize the fact that the microscopic picture in the human kidneys as well as in the kidneys of the experimental animals could not be distinguished from that in bichloride poisoning. The tubular degeneration is quite as intense, and the calcification of the tubules is quite as characteristic. The site of the degeneration and of the calcification was in the spiral and terminal straight portions of the primary convoluted tubules, the identical portion which is involved in bichloride poisoning. When the first case came under observation, the microscopic sections of the kidneys made us feel sure that we were dealing with a case of bichloride poisoning. We thought that the gastric tetany and the gastric symptoms might even be due to the same cause. Fortunately the patient had been observed clinically by Dr. Zeman before being sent to the Hospital, and Dr. Zeman was able to ascertain very positively that there was no suspicion of bichloride poisoning. Chemical analyses also failed to demonstrate the presence of mercury. Subsequent cases were therefore recognized as definitely not due to bichloride. The rôle that the alkalosis plays in the production of the kidney degeneration is still an open question. The lesion almost regularly follows obstruction to the pylorus or upper duodenum.

DR. KNOX: I am very much interested in these reports, because I have done one autopsy which presented this same combination of lesions, and at the time I also regarded it as a case of chronic bichloride poisoning. The patient was an elderly man, who had been observed for some time, and in whom gastric ulcer had been diagnosed. I found an enormously dilated stomach with very obvious retention and an ulcer on the pylorus causing ob-

struction. The calcification in the kidney lesion was so extensive that we investigated the patient's history carefully and tried to obtain from his physician a history of treatment with mercury for a considerable period of time, but no such medication was known to have been taken.

MULTIPLE MELANOMATA OF BRAIN AND SMALL INTESTINE *

ALFRED PLAUT, M.D.

The patient, a white female fifty-two years old, developed in the two months prior to death a rapidly progressing brain disease. The symptoms were hammering headache, loss of memory, sudden onset of loss of speech, listlessness, and negativism. She had to go to bed because she could not keep awake; her mind became irrational. There were no localized symptoms, and no paralysis. The pupils were normal. The tendon reflexes were exaggerated; the abdominal reflexes lacking. The eye grounds showed choked disc. The spinal fluid was released in a steady stream. It was water-like, but had a faint yellowish trace; the globulin reactions were strongly positive; albumin 0.1 per cent., and Wassermann reaction negative; in the sediment several round cells were found with pycnotic nuclei and little protoplasm. The urine was normal; it did not turn black; it was not tested with ferri-chloride. The temperature was about 100, the pulse corresponding. The neck was slightly rigid.

Post-mortem examination showed normal spinal cord and meninges. The bones of the skull and the dura were normal; at different points brown or black, cyanotic, round and oval spots of different sizes were either to be seen through the pia and arachnoid, or caused them to bulge. The tumor surfaces varied from the size of a lentil to that of a quarter. Near the longitudinal fissure there were more and larger ones than in the lateral parts. At the convexity both hemispheres showed an equal number of tumors; at the base however the right side contained more and larger ones, the apex of the left temporal lobe was completely transformed into a soft brown-black mass and black masses were shining through the floor of the third ventricle. Near the edge of the left hemisphere of the cerebellum one small round black spot was to be seen on the surface; beside this the cerebellum seemed to be free from tumor. A horizontal cut was made through the whole brain; the cut surfaces revealed a walnut-sized tumor in the left optic radiation; a similar one near the cortex in the posterior part of the right parietal lobe; one the size of a hazelnut in the anterior part of the same lobe; an ovoid one of the same size in the right thalamus, and many small ones especially in the ependyma of the lateral ventricles. The hypophysis was normal; the epiphysis contained a black tumor in its anterior part. It was of almost normal size.

* Presented March 13, 1924.

In the lower part of the small intestine many black tumors protruded into the lumen; they had the form of a saucer, not only the few large ones, but even the very small ones. Two feet, six inches above the Bauhinian valve an especially large tumor was found in the center of a long invagination. No tumors were to be seen above the second flexure of the duodenum, and none below the Bauhinian valve. Near the attachment line of the very fat mesentery a discontinuous, fine, brown injection of the lacteals was found. In the omentum a few black tumors, apparently replacing lymph nodes, were seen.

In the lower part of the left lower lobe of the lung a walnut-sized ovoid, black, soft tumor caused the pleura to bulge. The suprarenal bodies were normal, macroscopically and microscopically. The amount of pigment in the hypophysis was normal. There were no tumors in the choroids or retinae (the posterior half of both eyes was taken out in the post-mortem examination).

The microscope gave no evidence concerning the origin of the tumor. The cells were so full of pigment that little or nothing could be made of their structure. In several parts of the brain only the walls of the blood vessels contained tumor cells; occasionally a single large pigmented cell was found in the perivascular space. The tumor in the epiphysis showed nothing in particular.

Amongst the manifold types of melanotic tumors, the infrequent cases like the one described above form a particular group with many tumors in the brain and intestine, and few tumors in one or the other organ. Davidson¹ described a case with many melanotic tumors in the brain and intestine, one large tumor in a suprarenal body and at the hilus of the lung, and several small ones in the lung. In 1921 in the Eppendorfer Krankenhaus in Hamburg a post-mortem examination was made, revealing many melanotic tumors in the small intestine and brain, and tumors of the same kind in the ovary and suprarenals. A melanotic tumor of the epiphysis was demonstrated by Ogle;² but this case is probably not a plain melanoma.

It is interesting indeed to know that in certain lower animals the central nervous system or the intestinal tract are the only organs which contain chromatophores,³ but even so we are at a loss to explain just why the small intestine is a seat of so many tumors or why the spinal cord remains free.

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Discussion:

DR. DAVID SMITH: I have worked with pigmented tumors at intervals for several years under Bloodgood in Baltimore, and this case interests me greatly. I would like to say a few words about the cells from which melanomas arise, as we found them in Baltimore. This is a most remarkable case. In 125 cases of pigmented tumors in Bloodgood's laboratory, there is no exact duplicate of this one. There were cases of pigmented tumors which metastasized to the brain, but none like this in which the pigmented nodules were present in the small intestine.

Pigmented tumors can arise, apparently, wherever there are pigmented cells, and if we search through the body, we find pigment cells in certain definite regions always, and in various other locations occasionally. We always find pigmented cells in the basal layer of the skin of the negro, and apparently the basal layer of the skin of the white race is capable of producing pigment under abnormal conditions. Cells, epithelial in origin, can give rise to a pigmented tumor that is considered a melanotic cancer. There are pigmented cells beneath the epithelium in the subepidermal tissue capable of giving rise to moles of a peculiar type, and later to melanotic tumors of a definite melanosarcoma type. In 300 benign pigmented moles we found eight or nine of this type. We find in the dermis beneath the basal layer of the skin little isolated cells. Sometimes these cells show branching processes. They have small round granules in their cytoplasm and morphologically are identical with the pigmented cells in the choroid of the eye. In one of these cases we found this picture, which is usually that of a benign growth, but on one edge of the section the cells had changed their character and become larger and more pigmented, giving the appearance of a melanotic sarcoma, just as it appears in the choroid of the eye. So apparently there are pigmented tumors arising in the subcutaneous tissue with all the characteristics of the pigmented cells in the choroid of the eye and these may give rise to melanotic sarcoma. I think perhaps in studies of this kind we may settle the question which is discussed in the excellent chapter on Melanoma in Dr. Ewing's book as to whether all pigmented tumors are epithelial or mesothelial in origin. We will probably find that both sides are right, and that some of the pigmented tumors are epithelial and others are mesothelial, and arise from the pigmented cells of the type found in the choroid of the eye and in these subepidermal nodules. I do not think that any of the studies we have made would throw any additional light on the origin of the tumor presented tonight, however.

DR. PLAUT: Both eyes were taken out, and there was nothing which pointed to a tumor of the choroid.

What Dr. Smith said about the skin brings up a point about the normal occurrence of melanotic pigment in the meninges. This does not correspond apparently to the distribution of pigment in the races. Long ago a doctor in the Dutch Indies made an investigation, and he came to the conclusion that the meninges of the Malayan people always contain a large amount of pigment, and those of the negro people do not. Virchow then made the ob-

servation that he found it always in the whites, and thought its absence in the negro improbable. I think this investigation is so easy to make that it is difficult to explain why there should be difference of opinion on this point.

A CLINICAL AND EXPERIMENTAL INVESTIGATION OF ARSPHENAMIN POISONING * †

SOMA WEISS, M.D.

*(From the Department of Pathology of Bellevue Hospital,
Dr. Douglas Symmers, Director)*

Cats were used in experiments designed to study the gross and microscopical tissue changes produced in the liver, spleen, and kidneys by arsphenamin, by arsphenamin combined with mercuric salicylate, and by arsphenamin administered after chloroform.

The results of these experiments indicate that repeated doses of arsphenamin, corresponding to massive therapeutic doses, produce small areas of necrosis, fatty infiltration, congestion with round cell infiltration, and occasionally cloudy swelling in the liver cells, with the evidence of fatty degeneration in the tubules of the kidneys in some cases. The poison produced no changes in the spleen.

This tissue injury was not increased or modified when arsphenamin was combined with mercuric salicylate, in amounts corresponding to therapeutic doses in man.

When the doses of arsphenamin mentioned were administered to cats in which liver injury had been produced by chloroform, the liver regenerated at the same rate as that in the series of cats which received chloroform alone. Arsphenamin, therefore, does not appear to increase the injury produced by chloroform.

The histological changes and the behavior of the poisoned animals do not correspond to those observed in acute yellow atrophy of the liver in man.

Toxic non-fatal accidents following the administration of

* The details of this investigation will be published elsewhere.

† Presented March 13, 1924.

arsphenamin to patients admitted to Bellevue Hospital during the last ten years, and arsphenamin fatalities occurring during the past six years in New York City are considered. The clinical behavior of the cases is discussed briefly.

Attention is called to the fact that the classification of the toxic reactions cannot be applied rigidly. Cases showing symptoms and signs characterized by skin reaction (dermatitis exfoliativa), and those with vasomotor reaction (edema) are relatively frequent.

Twenty-nine deaths at least are attributed to arsphenamin, but it is almost certain that more than that number have occurred in New York City during the past six years.

In twenty-one cases of the twenty-nine, death followed the injection of arsphenamin within a few hours. The liver showed no pathological changes in seventeen cases in which autopsy was held. It is important, however, to emphasize the fact that every case of the group showed severe chronic pathological changes in other organs.

Acute yellow atrophy of the liver, so-called, followed the administration of arsphenamin in eight cases, but no predisposing factor was found on pathological examination which explains the etiology of the disease.

Additional cases are mentioned in which death was attributed clinically to arsphenamin, but in which the autopsy revealed some other cause.

The toxicological analyses are recorded in seventeen fatal cases following the administration of arsphenamin.

It is concluded, on the basis of the study presented, that the majority of fatal accidents can be prevented by observing caution in individuals who show cardio-vascular and renal disease, clinical evidence of status lymphaticus, or acute infectious disease (pneumonia). The fact that animals, under the experimental condition described, do not show acute yellow atrophy similar to that in man, and that in the fatal acute accidents in which repeated doses of arsphenamin had been given the liver did not show noticeable pathological changes, suggests that thera-

peutic doses of arspenamin do not produce noteworthy tissue damages in the liver. One cannot attribute acute yellow atrophy of the liver to a direct toxic effect of arspenamin. However, as the close relationship between the administration of arspenamin and acute yellow atrophy is definite, the conclusion that arspenamin plays an *indirect* rôle in causing acute yellow atrophy is inevitable. One cannot say with certainty whether this rôle lies in the precipitation of the condition in the presence of predisposing causes or in the efficient bactericidal action of arspenamin whereby a toxin is liberated. The fact that the same disease occurs in syphilis without arspenamin suggests rather the second possibility.

I am indebted to Dr. Douglas Symmers for suggesting the problem and for valuable advice, and to Dr. Charles Norris, whose kind interest has made the analysis of fatal accidents possible.

Discussion:

DR. PLAUT: The increase in the cases of acute yellow atrophy in Europe after the war seems to point to the fact that there must be some underlying condition. It seems that salvarsan and other toxic agents provide the last momentum for the outbreak of the disease. In 1921 the increase in acute yellow atrophy in Germany and in Austria was very remarkable, but it is more remarkable that the pathologists coming from Switzerland and from Holland, countries which did not suffer by wartime conditions, reported a similar increase in cases of acute yellow atrophy, many of them without any sign of their having originated from salvarsan or other toxic agent. One case has been reported by Schmorl, who is certainly a very reliable observer, of a typical acute yellow atrophy which was started from poisoning by mushrooms. Generally mushroom poisoning (*Amarita muscaria*) is not similar to acute yellow atrophy, and the findings in the liver, as well as in the muscle, make it somewhat easy to differentiate between the two conditions, but Schmorl said that beside the cases of mushroom poisoning which gave the latter picture, there was one of acute yellow atrophy. In Holland in different parts of a small country where about the same conditions prevail, one pathologist reported a marked increase, and another reported no increase at all. All experiments and tests to find out a bacterial agent failed. I feel quite sure that there must be some underlying condition which is infectious in nature, or it may be a susceptibility, so that the proper stimulus only is needed to start acute yellow atrophy.

DR. EWING: I think Dr. Weiss's paper is a very important contribution, since he has backed up his conclusions with rather extensive experimental

studies and by very unusual clinical material. I hope that he will have his report in form for publication soon, and that it will be widely circulated. There is little doubt in the minds of most pathologists, and if there were any doubt I think the records of the Bellevue morgue and Dr. Weiss's paper would remove it, that salvarsan is perhaps the most dangerous drug ever introduced into medicine, not barring chloroform. This fact, if it is a fact, is no indication why it should not be used, but it emphasizes the great necessity of clinicians employing it very carefully and after taking all proper precautions. The very fact that in the average case of syphilis treated by salvarsan the careful physician examines the urine constantly for albuminuria, on the appearance of which he will slow up his treatment, indicates that the drug is an unusually toxic agent. Of course there are many explanations of the curious toxic reactions, the Herxheimer reactions, the jaundice, the liver damage, and the acute yellow atrophy, and it may be that its underlying cause is in the general nutrition of the patient. It may be that syphilis contributes the essential part of the underlying condition, and it may be secondary bacterial infection, and, what is still more likely, there may be variations in the character of the drug. Many have attributed this result to bad salvarsan. Whatever the cause, the fact remains that before salvarsan came in we did not see this type of syphilis, and since the advent of salvarsan, all over the world there have been reported cases of acute degeneration of the liver, the conclusion being fairly clear that salvarsan directly or indirectly is the cause of the damage. In my experience with the Army at Washington where we encountered material from the autopsies in the camp hospitals, salvarsan deaths, to say the least, were frequent. There was one man at the Museum in Washington who examined ten cases. There I think the lesions in the liver and in the brain were most characteristic. Capillary hemorrhages in the brain were constant, and I had the impression then that the liver was comparatively resistant and the brain one of the most frequent organs to be damaged by salvarsan. These general facts, and especially the records of the Medical Examiner's office in New York, seem to me to call for the frank acceptance of the conclusion that salvarsan is a dangerous remedy, and should be used with much greater caution than is now generally the custom, and that the toxic phenomena, whether passing or severe or fatal, should be referred to the salvarsan or arsenic. A year ago Denton examined very carefully quite a series of livers from the Bellevue Hospital cases, and with a very excellent histological technic, he was quite impressed by the constant occurrence of minor changes in the way of cell degeneration and vascular lesions which he thought were specific. I was not quite so fully convinced of the correctness of his conclusions, but his splendid technic certainly suggested that if one wished to search the body for lesions in salvarsan cases which showed no obvious gross changes, he might very well succeed in finding them.

DR. WEISS: Regarding the brain, I think it is very probable that the direct cause of the death is edema and hemorrhages. Grossly, in the cases which we studied we did not find this. However, it is a fact that death al-

most invariably occurred with convulsions and neurological signs, and it is very probable that the cause is cerebral.

Regarding the danger of salvarsan, I think Dr. Denton was very enthusiastic, and thought that salvarsan is a very dangerous product. When I began the investigation, it was with the idea that it was dangerous, and later I reached a stage where I thought it did no damage. After analyzing the cases I feel that if physicians would be careful and take all the necessary precautions in salvarsan administration and avoid massive doses, we would find only a very few cases of acute yellow atrophy. Salvarsan if used in small doses is no more dangerous a drug than many others. I think there are many other drugs the usefulness of which cannot be compared with salvarsan but following the use of which there are almost as many deaths.

A CASE OF RIEDEL'S STRUMA ASSOCIATED WITH REMNANTS OF THE POST-BRANCHIAL BODY *

(A CONTRIBUTION TO THE KNOWLEDGE OF CHRONIC THYROIDITIS)

LOUISE H. MEEKER, M.D.

(From the Department of Pathology and Bacteriology, New York Post-Graduate Medical School and Hospital)

Abstract †

Riedel's iron-hard struma is a form of chronic inflammation of the thyroid gland which has not received much consideration in this country from either the surgeon or the pathologist. The observations of Ewing are an exception to the general dearth in the English language.

The case we have to present was operated upon at the New York Post-Graduate Hospital by Dr. T. H. Russell, September 14, 1923. The patient was a well-developed man fifty years of age, apparently in good health.

The patient complained of a painless swelling of the neck that had existed four or five months and had gradually grown larger. His vision had been impaired for three months and his voice had been husky for one month.

Physical examination showed the eyes were slightly prominent, there was no tremor or tachycardia; the tonsils were enlarged, the throat congested, and there was a severe pharyngitis and tracheitis.

The thyroid gland showed a marked general enlargement, was very hard and only slightly fixed. The overlying skin was freely movable. The sub-

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† A fuller report with illustrations will appear in the first volume of the *Journal of Pathology*.

maxillary lymph glands were shotty. The clinical diagnosis was carcinoma.

At operation the entire thyroid gland was removed without great difficulty. Recovery was uneventful. Two months later tonsillectomy was performed.

The surgical specimen presented an almost symmetrical enlargement of both lobes, measuring in its entirety 19 x 6 x 4 cm. The external surface presented rounded prominences, but was smooth except for delicate fibrous tabs, remnants of the perithyroid adhesions. The consistency was very hard throughout and the cut surface was everywhere the same, yellowish white and homogeneous, showing thin translucent lines between small irregular opaque areas suggesting lobules. There was no colloid to be seen. Lymph glands attached to the centre of the anterior lower border measured 18 x 7 x 5 mm. They were firm and, on section, pinkish-white with hemorrhagic markings.

Microscopic sections showed a striking change in the thyroid structure. The capsule was thickened, its blood vessels engorged and surrounded by dense collections of inflammatory cells. In the substance of the gland there was a remarkable abundance of fibrous tissue irregularly arranged in wide septa with smaller fascicles crossing between them in every direction. Interspersed in this fibrous tissue there were both diffuse and circumscribed collections of inflammatory cells, scattered lymph follicles, and in widely separated areas, remnants of the gland lobules. The scattered parenchymatous cells appeared as vesicles containing colloid, as collapsed vesicles or as small clumps or strands. Occasionally these epithelial cells were well preserved and a few were found in mitotic division.

Peculiar nests of well-preserved epithelial cells were found in some of the sections. These nests were of various shapes, occurred singly or in groups and very rarely possessed a lumen. The cells were large, polyhedral or flattened and the nuclei were oval and vesicular. We have identified these cells as the glandular parenchyma of the post-branchial body as described by Getzowa.

The patient's tonsils, which were removed two months later, showed increase of lymphoid tissue and marked chronic tonsillitis with fibrosis and peritonsillitis with thrombosed blood vessels. The lymph glands attached to the thyroid showed chronic inflammation.

Hermann and Verdun insisted that this body disappeared in human adults. Getzowa found it in adult thyroid glands four times, in three cretins and one idiot. Hermann and Verdun thought it possible that pathological observations might help to elucidate the mooted question of the relation of the post-branchial bodies to the thyroid gland in man. Getzowa found a struma post-branchialis and Langhans attributed certain carcinomas to this origin. The possible relation of these post-branchial remnants to Riedel's struma appears not to have been considered hitherto.

In the literature there are reports of twenty-eight cases of Riedel's struma.

This peculiar struma occurs usually in females, as a rule before the 40th year, and commonly both lobes are affected. The duration of the disease is usually brief, from a few weeks to six months, and there is usually a record of previous good health. More than half the cases are characterized by dense adhesions about the trachea and large vessels and nerves. Pressure may give rise to attacks of acute distress.

The tumor-like growth is very hard, compared to iron by Riedel, to cartilage by Tailhefer, to bone by Ricard and to wood by the French authors.

The size varies greatly; the shape is usually like the thyroid but may be slightly nodular. Rarely it is engrafted on a previous goitre.

With few exceptions the preoperative diagnosis has been carcinoma. The retrogression after extirpation has been the striking clinical manifestation while the diagnosis of non-malignancy upon microscopic examination has been equally surprising.

Histological descriptions agree with few exceptions in essential details with that of Riedel. Murray compared his case with an advanced case of myxedema, and Hashimoto found chiefly lymph follicles and called his cases struma lymphomatosa. They were rather an early stage of Riedel's struma, as pointed out by Ewing.

Anatomically the disease is characterized in its early stage by hyperplasia of the parenchyma and later by a chronic inflammatory infiltration by lymphocytes, plasma cells and eosinophile leucocytes with slight inflammatory changes on the part of the vessels. True lymph follicles are abundant especially in the earlier stages. As a result there is extensive degeneration of the parenchyma and proliferation of fibrous tissue which is present in remarkable amounts in the late stages. This inflammatory reaction may extend far beyond the limits of the gland.

Our own case lacks the extensive peristrumitis, the interstitial

hemorrhages, giant cells and eosinophile leucocytes seen by some authors.

In this case, however, we have evidence of regeneration by the parenchyma, a point recently denied by Reist, and we have the post-branchial remnants which have not previously been found.

Do these remnants, the parenchyma and accessory cysts, of the post-branchial canal system furnish a vicarious duct system by which infections may travel from the pharynx, and are the associated thyroid glands of low vitality as in cretins?

If they should prove to be a constant feature of Riedel's struma their presence might offer a solution of its peculiar pathology and incidence.

Discussion:

DR. EWING: I feel that Dr. Meeker is to be congratulated, and the Society as well, for this splendid study and contribution to the pathology of a not so very rare condition. She, with great labor, has done what I should have done in writing up the subject for the second edition of my book: looked up the literature thoroughly and presented in adequate form the whole subject. My contribution, if it was a contribution, consisted in simply identifying Hashimoto's malignant lymphoma, which has no hyaline or fibrous tissue in it, with Riedel's iron-hard struma, an interpretation which I thought was justified by the fact that I possessed in my small collection intermediate stages. Dr. Meeker's contribution on post-branchial epithelial cell rests seems quite important, although I am not optimistic that its proved relation to the post-branchial body would be of great aid in elucidating the causation of the disease.

There are some practical points which I think are very striking. One is that in spite of the enormous experience of American surgeons in removing goitres for many years, this is the first formal contribution in the American literature, and since it is not conceivable that many cases are not observed, the conclusion must be that they are not recognized. The second point is that if one who has not seen this disease should encounter it under the microscope he would very likely be induced to give a diagnosis of malignant tumor, because the histology is quite puzzling. In some of my cases such a diagnosis was ventured with some caution by very experienced microscopists. Another point I would like to emphasize, perhaps prematurely, is that the cellular forms of this disease are extremely responsive to radiation. One case was very promptly aided by that agent, while I think the fibrous forms will be quite resistant.

ANEURYSMAL DILATATION OF THE PULMONARY
ARTERY WITH PATENT DUCTUS ARTERIOSUS
BOTALLI. DEATH FROM RUPTURE OF ANEU-
RYSM INTO PERICARDIAL SAC *

G. L. MOENCH, M.D.

(From the Office of the Chief Medical Examiner of the City of New York)

Abstract †

The case presented and the specimen demonstrated was one of saccular dilatation of the pulmonary artery with a maximum diameter of about three inches. Death occurred suddenly from rupture of the aneurysm into the pericardium. There was a patent ductus arteriosus Botalli which admitted the index finger. The pulmonary valve had but two leaflets. The cusps of the mitral valve, especially the aortic, were thickened.

Aneurysm of the pulmonary artery is quite rare and the case presented is the only one in the records of the office of the Chief Medical Examiner of the City of New York in the past six years; that is, among about 65,000 cases, with approximately 10,000 autopsies.

A considerable number of cases are, however, reported in the literature. Henschen in 1906 collected forty-two cases and Posselt in 1909 some additional ones. Since then single cases have been reported by various authors.

As far as the etiology of pulmonary aneurysm goes, one of the most important factors seems to be a patent ductus arteriosus; syphilis is a disputed point. Age is not so important as in aortic aneurysm and, contrary to aortic aneurysm, pulmonary aneurysm is more frequent in females. Unusual as it may seem, dilatations of the pulmonary artery rarely cause sudden death.

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† Published in full in *Jour. Am. Med. Assn.*, 1924, lxxxii, 1672.

A LARGE INTRA-ARTICULAR TUMOR OF THE KNEE
JOINT. REPORT OF A CASE OF FIBRO-ENDO-
THELIOMA ARISING FROM SYNOVIAL
TISSUE *

LEWIS CLARK WAGNER, M.D.

An adult, thirty-five years old, a musician, with an irrelevant family and past history, without any apparent cause, three and a half years ago began to complain of pain in the right knee. It was treated with the usual rheumatic treatment by the family physician but with no improvement. In the summer of 1923, he consulted a surgeon and the limb was immobilized in plaster without any relief of symptoms.

The patient came under the care of Dr. Gibney and myself in October, 1923. Examinations showed him to be in good condition but he was walking with a slight limp, although the functions of the right knee were not im-



FIG. 1. X-ray showing the outline of the tumor.

paired. There was one inch difference in the measurement of the knees, with a slight fullness under the right patellar tendon, which was slightly tender. He brought a report of x-ray findings which were normal, although I did not see the pictures. The case was thought to be one of chronic synovitis

* Presented March 13, 1924.

especially of the retro-patellar sac, and was treated conservatively with cautery and strapping. He did not improve but rather the pain became worse and extremely so in wet weather, so that it required codeine for relief.

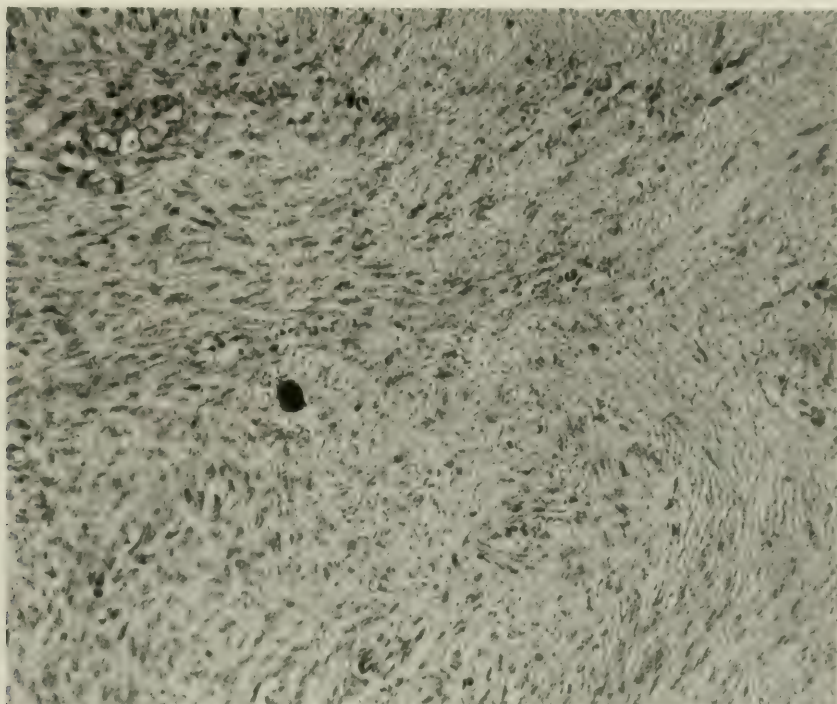


FIG. 2. Photomicrograph of tumor showing peculiar elongated blunt cells lying closely together. Occasional mitotic figures are found.

In January, 1924, an *x*-ray was taken, which showed a mass behind the patellar tendon that was thought to be hypertrophied synovial tissue, but a definite tumor was not considered. On looking back it can easily be recognized.

On February 13, 1924, the patella was split and the knee joint exposed. A solid tumor covered by a synovial veil lay in the knee joint. It was attached to the outer antero-inferior border of the capsule by a small attachment. The tumor was so large that it was divided longitudinally to facilitate removal and shelled out with little difficulty. The knee joint was normal otherwise. The tumor measured 7 x 5 x 3 cm., was elliptical in shape, and surrounded by a definite capsule. It was hard, and a diagnosis of benign fibroma was made from the gross examination. Under the microscope the tumor shows peculiar, elongated blunt cells lying close together. Mitotic figures, although few, were seen. It was thought to be a very atypical fibrosarcoma, but I believe it is a fibroendothelioma arising from synovial tissue. The prognosis should be very good.

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Discussion:

DR. EWING: I should think that the diagnosis of fibro-endothelioma was probably correct. In the last picture shown there were groups of isolated cells which would hardly be consistent with a fibroma, and which had a somewhat polyhedral form. I would not venture to make a diagnosis on the lantern slide, if I had not seen in the past three months three cases very similar to this one, one from Dr. Bloodgood, one from Dr. Smith of Harvard, and another one of our own. They show quite a variety of structures, but in a general way the picture approaches the case which Dr. Wagner has just presented. The position of the tumor is strongly suggestive of an origin from the endothelial cells lining a bursa. There is no doubt that the bursal endothelium is capable of extensive proliferation producing tumors of this same general character.

DR. CORNWALL: Were the tumors always benign?

DR. EWING: No; one of the cases metastasized and proved malignant.

DR. WAGNER: I think Dr. Ewing saw this section. I cannot find very much in a cursory review of the literature, but I did find one definite case similar to this called a fibro-sarcoma reported by Marsh in a London surgical journal in 1898. He operated on this case in 1893 and removed a tumor about half the size of this. A year later he operated again, and he called this a recurrence. Two years later it recurred in the scar and then one year later the tumor occurred in the popliteal space, and at this time he amputated the leg because of the repeated operations.

LESIONS OF THE AORTA ASSOCIATED WITH ACUTE RHEUMATIC FEVER AND WITH CHRONIC CARDIAC DISEASE OF RHEUMATIC ORIGIN * †

ALWIN M. PAPPENHEIMER, M.D., AND

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(From the Pathological Laboratory of the Presbyterian Hospital and College of Physicians and Surgeons, Columbia University, New York)

The question has frequently arisen as to whether the unknown virus of acute rheumatic fever may localize in the aorta. An abundant clinical literature exists on this subject, but there are few definite data from the standpoint of histological pathology.

The first serious histological study of the lesions in the aorta, and to our knowledge the only one, is that of Klotz (1912),¹ who reported his findings in a series of fifteen cases of various ages, giving a history of one or more attacks of rheumatic fever, associated with progressive or recurrent heart disease.

In the acute cases he found that the arterioles of the media were more prominent than usual and the nutrient vessels encroached beyond the outer third of the media. Edematous perivascular infiltrations of lymphocytes and plasma cells were constantly found. The elastic fibres in their vicinity were interrupted, often appearing as if mechanically broken. The muscle elements in the neighborhood of the vasa vasorum had also disappeared.

In addition there were extensive infiltrations of inflammatory cells in the adventitia. Lymphocytes and plasma cells were diffusely scattered through the tissue, while more densely aggregated cells were seen about some of the vessels. Polymorphonuclear leucocytes were present in relatively small numbers. Occasionally areas of endothelial proliferation were observed in the vicinity of small capillaries and in some of the sections, fibroblasts were seen.

* This article will appear in an early issue of the *Journal of Medical Research* in greater detail, and with illustrations.

† Presented April 10, 1924.

In the recurrent and chronic cases, the same cellular infiltrations were found but it was noted that the vasa vasorum were quite frequently present in the middle third of the media and they were surrounded by an "excessive amount" of fibrous tissue. In cases of long standing, nodular intimal thickenings, fibrous rather than atheromatous, were present.

Klotz concludes from his study that there is a fairly definite form of arterial disease associated with rheumatic fever in its different stages. The arteries react to the irritant in a true inflammation, and this reaction is observed in the adventitia and the outer portion of the media, beginning in the neighborhood of the smaller arteries. During the acute process the fixed tissues about the smaller arteries are damaged or even destroyed. With repair there is left a patchy fibrosis, leading to loss of elasticity and diffuse dilatation.

He compared the process with syphilitic mesaortitis, and pointed out that in the latter condition there is greater lymphoid infiltration, frequent gummatous necrosis and the formation of granulomatous tissue in the areas of greatest reaction. The invasion of the capillaries toward and into the media is more marked in syphilis and the nodular thickening of the intima more extreme.

The following year Klotz described another case, under the title of "Arterial Lesions in Rheumatic Fever,"² which from the description is undoubtedly a case of bacterial endocarditis. This second publication probably delayed the acceptance of the accurate and well-founded observations described in the first.

A study of the finer histology of the myocardial and subcutaneous lesions beginning with Aschoff's³ description of the "submiliary rheumatic nodules" has added materially to the understanding of the pathology of the disease and has furnished new criteria for identifying rheumatic lesions encountered in other organs.

MATERIAL AND METHODS

In the selection of cases for the rheumatic group, we have based the diagnosis upon (1) a clinical history of one or re-

peated attacks of rheumatic fever or of chorea, or of repeated attacks of tonsillitis, (2) upon the finding of typical rheumatic lesions at autopsy, namely, verrucous endocarditis, showing the characteristic structure, and absence of bacteria in sections, (3) Aschoff bodies in the myocardium associated in the recurrent cases with elliptical perivascular areas of fibrosis, (4) fibrinous pericarditis, or pericardial adhesions, and (5) chronic mitral disease, not arteriosclerotic. Not all these criteria were at hand in every case; in a number of instances, in which typical Aschoff bodies were present in the myocardium, there was no history of a previous rheumatic infection.

All of the cases included in the rheumatic group gave a negative Wassermann reaction during life, as well as a negative luetic history.

The collection of a control group presented certain difficulties. Aside from the possibility that other infectious diseases, such as scarlet fever, might produce changes in the aorta indistinguishable from those of rheumatism, it was difficult to exclude entirely the occurrence of a previous unrecognized rheumatic infection.

The possible syphilitic factor in the control group was excluded by including only cases with negative luetic history and negative Wassermann reaction. However, a series of aortæ showing characteristic syphilitic lesions was studied for comparison with the rheumatic group.

Table I gives the age distribution in the rheumatic and control groups, respectively.

The sections were studied with (1) hematoxylin-eosin, (2) with Weigert's elastic tissue stain, followed by hematoxylin and Van Gieson's picrofuchsin, (3) with Unna-Pappenheim methyl-green-pyronin method. The last stain was particularly useful for demonstrating the specific "Aschoff cells," plasma cells and bacteria.

GENERAL DESCRIPTION OF THE LESIONS

Intima: No lesions were found which could be definitely ascribed to rheumatic infection, or differentiated from the

changes of ordinary atherosclerosis. It was not unusual to find pronounced intimal fibrosis even in relatively young individuals, but this occurred with equal frequency in the control group. In some of the atherosclerotic plaques, the young connective tissue cells stained intensely with pyronin, but did not in other respects imitate the morphology of the Aschoff cells.

Media: One of the lesions that forced itself upon our attention early in the study was a marked irregularity of size, shape and distribution in the muscle nuclei. Often there were present areas in which the nuclei were sparse or entirely wanting. When the sections were studied with the elastic tissue Van Gieson stain, it was seen that the muscle fibres in the corresponding regions of nuclear depletion were absent, their place being taken by the condensed collagen and elastic fibres. The areas had not the appearance of scars resulting from previous localized inflammatory lesions, inasmuch as the elastic lamellæ were intact and not disarranged. They suggested rather a localized atrophy and disappearance of the muscle fibres, such as might result from long continued interference with the blood supply. We are inclined, therefore, to ascribe these changes to the alteration in and about the nutrient vessels, rather than to a direct action of the rheumatic virus upon the medial wall.

That these changes are correlated, directly or indirectly, with the rheumatic infection is strongly indicated. They were found with much greater frequency and intensity in the rheumatic series than in the control group.

Of much greater interest and diagnostic significance are the alterations found about the nutrient arteries. Normally, these do not penetrate beyond the outer third of the medial coat; they are clothed in a rather delicate connective tissue adventitia, the collagen fibres of which run parallel to the long axis of the vessel. They are unaccompanied by wandering cells. The muscular and elastic fibres end abruptly and evenly as they reach this connective tissue sheath.

In the rheumatic cases, the nutrient vessels were surrounded by broad compact masses of connective tissue, which accom-

panied the smaller branches, and were prolonged into irregular strands penetrating the neighboring musculo-elastic tissue. These scars having roughly the shape of an inverted wedge about the penetrating vessels, with their prolongations into the adjacent tissue, we have come to regard as the most characteristic alteration of the media. That they are true cicatrices is shown by the finding of swollen and fragmented remains of elastic fibres amongst the connective tissue fibrils. By analogy with the myocardial lesions, we were led to assume that these scars marked the site of previous focal perivascular inflammatory lesions, comparable to the Aschoff nodules about the small branches of the coronary arteries. We sought diligently for these earlier lesions; and in a number of instances, found cellular infiltrations. The elements composing them were difficult to identify with certainty. The predominant cell type was somewhat larger than a plasma cell, and much more irregular in shape. The excentric nucleus was sometimes spherical, more often distorted, and stained intensely and diffusely. It did not show the cart-wheel arrangement of the chromatin found in the typical plasma cell. Rarely the cells contained two or several nuclei. The cytoplasm showed a striking affinity for basic stains, so that these cellular foci stood out sharply with the methyl-green-pyronin stain. Frequently these cells appeared to be undergoing regressive changes, and fragments of their protoplasm were detached. The cells in question, therefore, resembled plasma cells in their staining reaction, and clasmatocytes or adventitial wandering cells in this property of extruding cytoplasmic fragments. As to the precise identity of these cells, we hesitate to commit ourselves.

A certain proportion of typical small lymphoid cells could be positively identified. In none of our preparations did we find in the media large multinucleated elements, such as enter into the formation of the Aschoff bodies. It does not seem to us that this necessarily contradicts the idea that these perivascular cell infiltrations represent a focal reaction to the rheumatic virus. We shall discuss this more at length below. Leaving aside for

the moment the question of their pathogenesis, what evidence is there that these perivascular lesions are of rheumatic origin?

Scars were present in 38.1 per cent. of the rheumatic group as compared with only 9.1 per cent. of the control series—a difference which is surely significant. Cellular infiltrations of the type described were found in 32.8 per cent. of the rheumatic cases, and in 11.7 per cent. of the controls.

Adventitia: Whatever doubts may arise as to the specificity of the medial changes described above, there can be no question that the rheumatic virus may, in certain cases, produce characteristic focal alterations in the aortic adventitia.

In one case, in the adventitia were found several miliary nodules, of which the most conspicuous cellular constituents were large oval or rounded cells, some with a single nucleus, others containing as many as ten. The cytoplasm of these cells was basophilic, staining intensely with pyronin. The nucleus had a very distinct nucleolus. The cells seemed to be arranged about degenerating elastic or collagen fibres. They resembled the Aschoff cells in all respects, save that they were somewhat more rounded and sharply outlined. There were a few lymphocytes and plasma cells nearby.

In several other instances typical Aschoff cells showing, however, little tendency toward a nodular grouping were found with the methyl-green-pyronin stain. They were absent in all the control non-rheumatic cases and when present may, in our opinion, be regarded as diagnostic.

The other alterations found in the adventitia are less characteristic, but nevertheless, they occur with so much greater frequency and intensity in the rheumatic than in the control group that they may be looked upon as part of the reaction to this infection. Our observations in general confirm those reported by Klotz in his first paper. There are found loose or more compact aggregations of plasma cells and lymphoid cells, sometimes concentrated about the vasa vasorum, sometimes more loosely scattered through the connective tissue. The endothelial cells of the smaller vessels often appeared swollen, and their cyto-

plasm showed a marked affinity for the pyronin stain. This alteration, however, appears not to be specific, and has been frequently observed in the control series.

A sclerosis of the smaller nutrient vessels was present at times, but was not a constant finding, and we are doubtful as to its significance.

Definite fibrous thickening of the adventitia, as a whole, is recorded more frequently in the rheumatic series than in the controls (15.9 per cent. as compared with 1.3 per cent.). It may be regarded as the sequel to the long continued or repeated inflammatory process, and occurs with the same frequency as the Aschoff cells.

The demarcation between media and adventitia was obscured in 19.8 per cent. of the rheumatic cases by the interruption of the outermost layers of elastic fibres and the fusion of the medial connective tissue with that of the adventitia.

DISCUSSION: PATHOGENESIS OF THE LESIONS

A complete understanding of the alterations brought about by the agent of rheumatic fever will not be possible until the inciting agent can be demonstrated in the lesions. Certain general considerations as to the nature of the changes produced in the myocardium and valves may, however, be helpful toward interpreting the alterations found in the blood vessels.

In the already extensive literature dealing with the finer histology of the Aschoff bodies, most of the emphasis has been placed upon the peculiar cellular reaction, and particularly upon the appearance and origin of the large, often multinucleated cells which are so distinctive a feature of the lesion. It has seemed to us, and this has been suggested also by Thorel⁴ and others, that the initial, and also the fundamental injury consists in a swelling, fragmentation, and lysis of the collagen fibrils, usually in the vicinity of small arteries, but sometimes, as in the substance of the heart valves, in areas not topographically related to the blood vessels. This fragmentation of the connective tissue is invariably present in the centre of the Aschoff nodules, and one has the impression that the cellular changes are secondary to it.

Mitotic figures have never been described in the large cells, nor have we found evidence of active proliferation of these elements. Their multinucleated character is either due to fusion of cells, which seems unlikely, because of their isolated detached occurrence; or to amitotic division, which is suggested by the lobulated appearance of the nuclei in some cells. As to their derivation, whether from pre-existing connective cells at the periphery of the lesion or from adventitial cells which have migrated from the neighboring vessels, we are unable to decide. The occasional presence of the cells in the pericardium, and the adventitia of the aorta make untenable the view of Whitman and Eastlake⁵ that these cells arise from degenerating muscle fibres.

Whatever their origin, these cells, conspicuous as they are, are but one element in the reaction to the primary connective tissue injury; and since they are probably transient, frequently showing regressive changes in their nuclei, it is at least doubtful whether they play an active rôle in the cicatrization of the injured area.

We have recently, however, had occasion to study sections taken through the mitral valve in a case of acute rheumatic endocarditis and myocarditis. In addition to the verrucæ on the surface, one could see in the substance of the valve focal areas in which there was swelling and fragmentation of the connective tissue fibres, with a slight change in their staining reaction. About these degenerated areas, the connective tissue cells were swollen and basophilic, but there were no typical multinucleated Aschoff cells, nor lymphoid accumulations, and one could hardly speak of the lesion as a rheumatic nodule.

Thalhimer⁶ in a recent paper states that he has never found Aschoff bodies or cells in the vegetations, in their base or in the valves. This is in accord with our own experience. It is highly probable, therefore, that the reaction to the virus varies somewhat according to the tissue in which it is localized.

In describing the cellular infiltration about the nutrient vessels of the media, it was stated that no typical Aschoff cells were

encountered. From the foregoing discussion, it seems not improbable that the reaction, so far as the cellular components are concerned, resembles that in the substance of the valve, rather than in the myocardium. In the adventitia of the aorta, as has been described, typical submiliary nodules with cells of the Aschoff type may be present.

Another point of interest is the absence of new-formed blood vessels in the healing scars of a rheumatic focus. The lesion throughout is avascular, and the final cicatrix is distinguished by its compactness and the absence of blood vessels. These features are as striking in the aortic lesions as those in the myocardium, and differentiate them from healed or healing syphilitic lesions.

There are several features in which the lesions described in the aorta differ from those produced by syphilis. As Klotz has already pointed out, the cellular infiltrations, both in the media and adventitia, are sparse in comparison to the very abundant lymphoid and plasma cell accumulations found in syphilis. Furthermore, the rheumatic scars remain confined to the vicinity of the normal penetrating vessels. The syphilitic granulation tissue is attended by the formation of new capillaries, and the scars which result are far more extensive and lead to far greater disruption of the elastic and muscular fibres. Again, since the rheumatic lesions are limited to the vicinity of the pre-existing vessels, they are rarely found deeper than the junction of the middle and outer thirds of the media. The syphilitic lesions frequently extend to the intima.

Another observation which is helpful in differential diagnosis is that the connective tissue in the syphilitic scars is not so dense and acellular as that produced in rheumatism.

SUMMARY

A comparative histological study of the aorta has been made in a series of seventy-six rheumatic cases, and in seventy-seven non-rheumatic cases, dying from a variety of diseases. An equally large series of syphilitic aortitis cases was studied for comparison.

Certain lesions were found in a much higher percentage of the rheumatic cases than in the controls, and so far as our observations go, appear to be characteristic of rheumatic infection.

The most distinctive lesions were: (1) Dense scars in the vicinity of the nutrient vessels, often acellular; (2) Aschoff cells or nodules in the adventitia.

Further study is necessary to determine the distribution of the lesions in the aorta, the possible occurrence of similar changes in peripheral vessels, and their clinical significance.

TABLE I

Age Incidence

	Rheumatic	Control
Under 10 years.....	9	6
11-20	17	11
21-30	16	10
31-40	11	15
41-50	10	7
51-60	7	11
61-70	5	11
71-80	1	6
	—	—
	76	77
Males	33	40
Females	43	37

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1. KLOTZ: *Trans. Assn. Am. Phys.*, 1912, xxvii, 181.
2. Ibid.: *Jour. Path. and Bacteriol.*, 1913, xviii, 259.
3. ASCHOFF: *Verhandl. d. deutsch. path. Gesellsch.*, 1904, viii, 46.
4. THOREL: *Erg. der Allg. Path. u. Path. Anat.*, 1910, xiv¹, 2.
5. WHITMAN AND EASTLAKE: *Arch. Int. Med.*, 1920, xxvi, 601.
6. THALHIMER: *Arch. Int. Med.*, 1922, xxx, 321.

Discussion:

DR. MOSHCOWITZ: Do you find these lesions only in early cases of rheumatic fever in the aorta or the myocardium, or in patients who have given a history of having had rheumatism many years previously?

DR. PAPPENHEIMER: We find cases in which, from the history, the rheu-

matic infection occurred many years ago. There is no relation between time of incidence of the infection and the character of the lesions, nor can one say that the cases in which we find the Aschoff bodies were more recent than those where we found only the scars. But the same thing holds for the Aschoff bodies in the myocardium. We have found acute lesions in the myocardium in patients who have given no history of joint rheumatism, or who have given a history which dates back thirty years or more.

SYPHILITIC AORTITIS AND ACUTE RHEUMATIC MYOCARDITIS; REPORT OF TWO CASES *

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The two cases to be reported here are examples of syphilitic aortitis and acute rheumatic myocarditis. In neither case was there a previous history of rheumatism, nor any symptoms to indicate rheumatic disease of the myocardium.

CASE I. E. M. (history 57804), age fifty-one years, male, was admitted to the hospital December 12, 1923, complaining of pain over the heart and in the left arm. His past history was negative other than three ulcers on the penis thirty-three years ago, not followed by secondary lesions as far as he could recall. He had been married twenty-three years, and his wife had had two miscarriages.

Present Illness: The onset occurred ten months ago, when shortly after rising, he had a sudden attack of sharp stabbing pain beginning over the precordium, radiating to the right infraclavicular fossa, and down the left arm to the hand. For the next three days there was a feeling of dull precordial soreness, with frequent returns of the sharp pain on exertion. He rested from work for three and a half months, and the pain disappeared. After this he returned to work, and was free from pain for three months. Two months ago, the attacks of pain returned, and have steadily increased in frequency. Slight exertion precipitates them, as does also overeating and mental excitement. Relief from pain is obtained when he ceases whatever he is doing and rests.

Physical Examination: Heart: A diffuse impulse was seen over the precordium. At the base and in the first interspace, dullness was considerably increased. A loud systolic murmur and a diastolic murmur were heard over the precordial area. The systolic murmur was loudest in the third interspace and was transmitted to the neck. The pulse was regular and collapsing; rate 78 per minute. The blood pressure was systolic 110, diastolic 20.

* Presented April 10, 1924.

The blood Wassermann was four plus, and the spinal fluid Wassermann was negative.

X-ray showed the heart enlarged to the left and the supracardiac shadow greatly widened.

The remainder of the physical examination was essentially negative.

He was given mercury salicylate and potassium iodide without any effect on the intensity of the pain. Following 0.2 gm. of arsphenamine, the pain was relieved to a certain extent; nitroglycerine also gave some relief. One month after admission he began to have cramp-like abdominal pain, without nausea or vomiting. The liver, which had not been enlarged, previously, was felt at the level of the umbilicus; it was tender and pulsating. The temperature varied from 100 to 101°. The heart sounds gradually became fainter, tic-tac in quality, with gallop rhythm. The abdominal and precordial pain persisted. His condition became progressively worse, and he died on January 17, 1924.

Autopsy 9468. Anatomical diagnosis: Syphilitic aortitis, with involvement of the aortic valve; aortic insufficiency; aneurysms of aorta; acute rheumatic myocarditis; chronic passive congestion of viscera; edema of lungs; hydrothorax, right; generalized arteriosclerosis.

Heart and Aorta: The pericardial sac contained 50 c.c. of clear fluid. The heart with the pericardial sac and aorta weighed 1,010 gm. On the anterior surface of the left ventricle was a large tendinous plaque, and a similar one was present on the left auricle. The epicardium elsewhere was thin and smooth. There was a small thrombus in the tip of the right auricular appendage. The tricuspid and pulmonic valves were thin and delicate. The wall of the right ventricle measured 4 mm. in thickness. The tip of the left auricular appendage was filled with a thrombus. The free margin of the mitral valve leaflets was slightly thickened; the chordæ tendineæ were normal. The papillary muscles and columnæ carneæ were somewhat flattened and atrophic in appearance. The myocardium was reddish-brown in color, very soft and flabby. The wall of the left ventricle varied from 9 to 16 mm. in thickness. Just beneath the aortic ring, the endocardium was thickened, forming inverted valve-like pockets, 0.5 cm. in length. The aortic valve leaflets were thickened, their free margins rolled and cord-like. There were abnormally wide spaces between the leaflets. The orifices of the coronary arteries were above the highest point of attachment of the valve cusps; they were not narrowed. The coronary arteries were normal throughout.

Beginning immediately above the valve ring, the ascending portion of the aorta was dilated into a large aneurysm, which was adherent to the parietal pericardium, and which, bulging over to the right, was adherent to the wall of the right auricle. When the auricle was dissected away, its wall was found to be very thin. The aneurysm had a thick wall except where it adhered to the auricle. Here, over an area 2 x 3 cm., it was quite thin. The intimal surface of the aneurysm was rough and wrinkled with many grey translucent plaques.

The aneurysm terminated abruptly at its upper margin, and was entirely

confined to that portion of the aorta within the pericardial sac.

In the remainder of the aorta, the intimal surface was roughened and mottled with innumerable, irregular, raised, yellow areas, and in the thoracic portion, mingled with these, were grey, translucent plaques with longitudinal wrinkling. At the level of the seventh dorsal vertebra was another aneurysm, 3 cm. in diameter, which had made a distinct depression in the body of the vertebra.

Microscopic Examination: Heart: Throughout the myocardium were numerous accumulations of large cells with basophilic cytoplasm (Fig. 1).

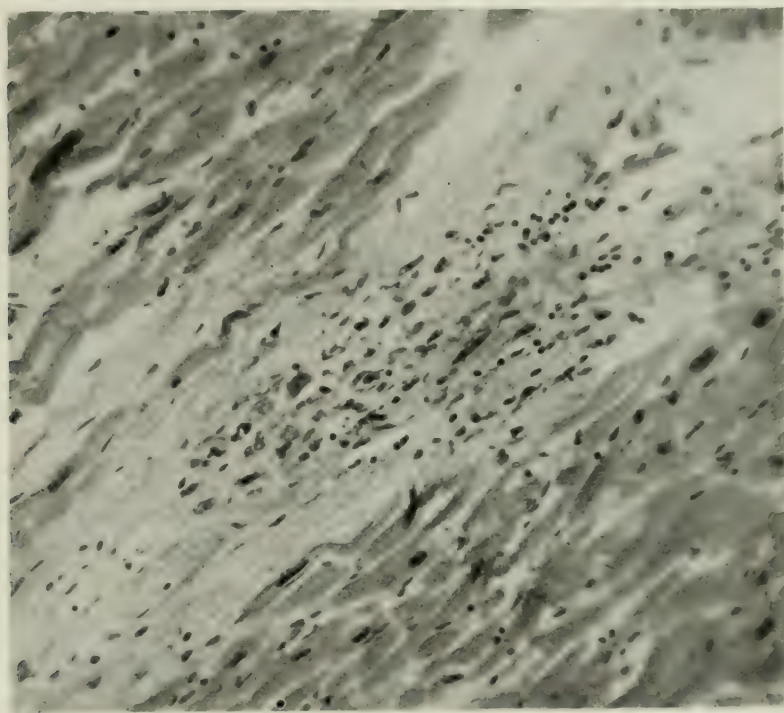


FIG. 1. Acute rheumatic myocarditis with Aschoff body. Autopsy 9468

The nuclei were large, at times indented, and each contained a single, large, deeply staining, somewhat stellate nucleolus. A few of these cells were multinucleated. In the central part of these cell collections, swollen fragments of connective tissue fibrils could be seen. These cell masses were usually situated in the adventitia of the blood vessels. The myocardium was hypertrophied, but there was neither scarring nor infarction.

Aorta: Sections from the aneurysm showed the intima to be thickened, and just beneath the endothelium were a few small round cells. In some places were small masses of calcium. Vessels were increased in number everywhere in the media, and dense mantles of small round cells and plasma cells surrounded them (Fig. 2). The elastic tissue fibres were interrupted at the site of the new vessels. The adventitia was increased in width, and about the vasa vasorum were masses of small round cells and plasma cells.

In sections from other portions of the thoracic aorta, the changes were the same, though not so intense.



FIG. 2. Syphilitic aortitis. Medial scarring with mononuclear cell infiltration. Autopsy 9468

CASE 2. J. H. D. (history 58730), age forty, negro male, was admitted to the hospital on December 16, 1923, complaining of heart trouble and shortness of breath. His past history and family history were negative.

Present illness began in July, 1923, with edema of the legs, dyspnea, and orthopnea. One month later he began to have attacks of paroxysmal, nocturnal dyspnea associated with a sense of precordial oppression. About a week before admission, he coughed up small amounts of blood.

Physical Examination: Respirations were Cheyne-Stokes in character. The lips were cyanotic. There was dullness with moist râles at both lung bases. The heart was enlarged to the left; the sounds of poor quality. At the apex was heard a blowing systolic murmur, and at the base a rough systolic and a blowing diastolic murmur. The blood pressure was systolic 170, diastolic 10. There was shifting dullness in the flanks. The liver edge was felt at the umbilicus. There was marked edema of the arms, legs, and genitalia. The blood Wassermann was four plus.

Though the edema subsided, the attacks of precordial pain and paroxysmal dyspnea became more frequent. On January 31st, he complained of some pain in the ankles, which was never intense and subsided after a few doses of sodium salicylate. His condition changed very little, and he died on February 6th, 1924.

Autopsy 9478. Anatomical diagnosis: Syphilitic aortitis, with involvement of the aortic valves; aortic insufficiency; cardiac hypertrophy and dilatation; chronic cardiac valvular disease; anasarca; chronic passive congestion of viscera; edema and infarction of lungs; atrophy of right kidney; compensatory hypertrophy of left kidney; acute rheumatic myocarditis.

Heart and Aorta: The apex rested against the left lateral chest wall, and the right border extended to the right costo-chondral articulation. The transverse diameter of the heart measured 21 cm. The epicardial vessels were enormously dilated. On the anterior surface of the right ventricle was a large area where the epicardium was thickened. The right auricle and ventricle were dilated. The papillary muscles and columnæ carneæ were hypertrophied. The tricuspid and pulmonic valves were thin and delicate. There was dilatation of the left auricle. The mitral valve was slightly thickened, and a few very tiny grey elevations were seen near the line of closure.

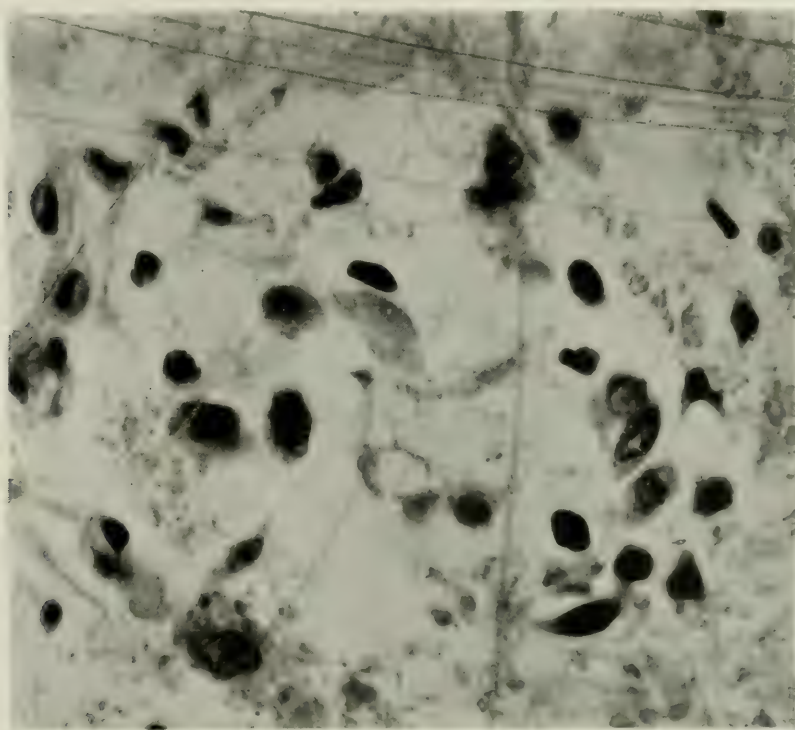


FIG. 3. Acute rheumatic myocarditis with Aschoff body. Autopsy 9478

The chordæ tendineæ were normal. The cavity of the left ventricle was much increased in size; the columnæ carneæ on the septal surface were somewhat flattened and slightly yellow. The columnæ in other parts of the ventricle and the papillary muscles were hypertrophied. The aortic leaflets were thickened and less flexible than normal. Between the cusps were abnormally wide spaces. The free border of the left posterior leaflet was cord-like and rolled over toward the sinus side. The upper margin of this cusp was 0.5 cm. below the upper edge of the other two leaflets. The free margin

of the right posterior cusp measured 22 mm. in length; that of the anterior 18 mm. The coronary arteries showed a few elevated yellow plaques in the intima without calcification or narrowing of the lumen. The orifices of these arteries were not narrowed. The myocardium was greyish-red; there was no scarring. The heart weighed 850 gm.

The intimal surface of the *aorta* was roughened by many elevated plaques, some grey and translucent, others yellow and opaque. In the arch of the vessel, the yellow areas were few in number whereas the grey, translucent plaques were quite numerous and there was some longitudinal wrinkling of the intima. The yellow plaques became more abundant as the bifurcation was approached, while the grey areas became less frequent and finally disappeared at the termination of the descending portion of the arch.

Other findings were an atrophic right kidney, without demonstrable obstruction of the ureter, hypertrophy of the left kidney, infarction and edema of the lungs, and chronic passive congestion of the viscera.

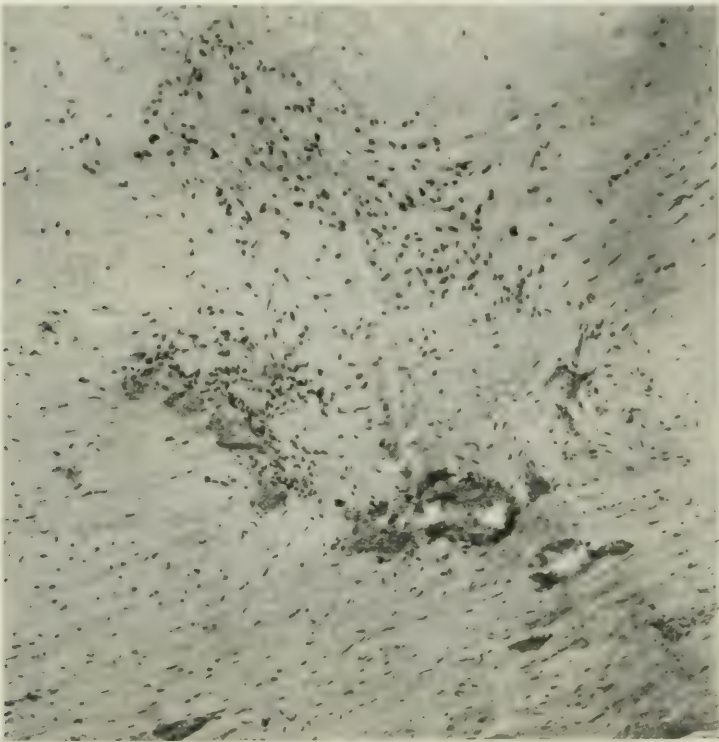


FIG. 4. Syphilitic aortitis. Scarring of media. Autopsy 9478

Microscopic Examination. Heart: The muscle fibres showed hypertrophy; there was no scarring. The blood vessels were markedly engorged; in the adventitia of some of the arteries were areas in which the connective tissue fibrils were swollen and fragmented, and about these were large cells having slightly basophilic cytoplasm and heavily staining vesicular nuclei, each with a large stellate nucleolus (Fig. 3). Some of these cells were undergoing fragmentation; others were multinucleated. These cell accumulations were quite numerous and occasionally about the margins of them were a few small mononuclear cells.

Aorta: The intima was thickened; in its deeper part were spaces where fatty material had been dissolved out. In the media and reaching into the adjacent part of the intima were blood vessels surrounded by loose mantles of small round cells, with a few plasma cells (Fig. 4). The elastic tissue fibrils were interrupted at the site of these vessels. About the normal penetrating vessels were a few plasma cells. The adventitia was thickened. Accumulations of small round cells and plasma cells were to be found about the vasa vasorum.

The changes in the aorta in these two cases are quite typical of those characterizing syphilitic mesaortitis. There is extensive scarring of the media, with the appearance of new vessels in the scars, surrounded by lymphoid cells and plasma cells. These vessels sometimes reach into the lower part of the intima. The elastic fibres are greatly interrupted and distorted at the site of the scars.

In the adventitia are characteristic dense accumulations of plasma cells and small round cells about the vasa vasorum.

There is no dense collagen about the normal penetrating vessels in the media as has been described in rheumatic aortitis,¹ neither could any Aschoff cells be found in the adventitia.

The lesions in the myocardium, composed of large cells with basophilic cytoplasm, sharply outlined nuclei, each with a prominent nucleolus, are identical with the submiliary nodules of Aschoff, now generally recognized as characteristic of rheumatic myocarditis.

Careful study of sections from many blocks of myocardium, from each case, stained by the Levaditi method, was negative for spirochetes.

We are indebted to Dr. Walter W. Palmer for the privilege of including the clinical records in this report.

References:

1. PAPPENHEIMER, A. M., AND VON GLAHN, WILLIAM C., *Proc. New York Path. Society*, 1924, xxiv, 61.

Discussion:

DR. LIBMAN: These observations are of considerable importance, and give increased experience in regard to intercurrent infections, mixed infections, and terminal infections, by the virus of rheumatic fever. We have had

examples illustrating all of these types. Clinically, I have seen cases which I believed represented mixed infections by syphilis and rheumatic fever, but I did not have the opportunity of obtaining pathological proof. We have observed at least four cases in which there was a combination of subacute streptococcus endocarditis and recent rheumatic infection as proved by the presence of Aschoff bodies. In cases of valvular disease of rheumatic origin in which there is no fresh endocarditis present, one may find recent Aschoff bodies. Terminal or intercurrent infections by the rheumatic virus may be encountered. In such instances there may be no clinical evidence of rheumatic infection. One observation relates to a patient who was operated upon for ruptured ulcer of the duodenum who had no evidence clinically of rheumatic fever. At the post-mortem examination the heart muscle showed recent Aschoff bodies and the valves a recent endocarditis of apparently rheumatic type. Another case was one of typhoid fever which, at post-mortem examination, showed a recent healing verrucous endocarditis of rheumatic origin as attested by the presence of Aschoff bodies.

I think that the observations of Dr. St. Lawrence at St. Luke's Hospital are very interesting in this connection. In a study of the familial incidence of rheumatic fever which he made he found that the familial incidence of rheumatic fever was just as common, or more common, than in the case of tuberculosis. Yet in cases of tuberculosis one makes an attempt to prevent other members of the family from getting tuberculosis. No one has thought of doing that in rheumatic fever. We have to regard the rheumatic virus as being around us all the time, and as acting like other infecting agents.

DR. VONGLAHN: These cases do show one of the things brought out by Dr. Libman, that in so many of our cases where we find post-mortem rheumatic pericarditis there is no history of previous rheumatic disease. In going over our rheumatic series with Dr. Pappenheimer both of us were impressed with the fact that the affection of the heart can continue for many years after a joint attack. I culled out of seventy odd cases seventeen in which the joint attack dated from one to thirty-eight years before the death without any subsequent joint involvement, and in these seventeen cases I found that there were typical lesions either in the endocardium, myocardium or pericardium, showing that the virus was still active.

DR. LIBMAN: Dr. VonGlahn called my attention to the fact that I had seen one of these cases clinically. Where was the aneurysm exerting pressure?

DR. VONGLAHN: Over the right coronary.

DR. LIBMAN: Dr. VonGlahn reminds me that I had suggested in that case that there might be present a lesion of the right coronary artery. The man was suffering from a right-sided insufficiency out of all proportion to what one would expect from a left-sided lesion and that was the reason why I suggested that there might be present some disease of the coronary artery.

DR. PAPPENHEIMER: I should like to ask Dr. Libman if he has studied at all the rheumatic lesions in the aorta, and if he has any views on the question?

DR. LIBMAN: I am sorry I did not see your pictures. I think that this is the first time that Aschoff bodies have been found in the wall of the aorta. I was very anxious to see the pathological material because these observations are of primary importance. We have, ourselves, observed vascular lesions (in smaller vessels) which are not due to involvement by Aschoff bodies. This observation of yours, however, would be the first absolute proof of rheumatic involvement of the aorta. Klotz described a rheumatic aortitis; one of his cases appears to be a subacute streptococcus aortitis. I think it would be very interesting to know in how far such a rheumatic lesion can compromise the coronary arteries. We have been finding a number of cases in which the symptoms of a valvular disease of the left side of the heart were complicated by the presence of narrowing of one or both coronary arteries. It is conceivable that we might get coronary narrowing from rheumatic disease alone or combined with atherosclerosis,—as well as from atherosclerosis alone.

EXPERIMENTAL CALCIFICATION IN MICE *

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There is a tendency for calcium to be deposited locally in necrotic tissue. It is also found in the aorta and other large arteries in arteriosclerosis, in old inflammatory exudates, thrombi, lungs, and bronchial lymph glands in tuberculosis, and renal epithelium in bichloride poisoning. Sometimes there is a more general deposition which gives rise to a condition known as "metastatic calcification." This was first described by Virchow in 1885, who pointed out that the lungs, the gastric mucosa, pulmonary veins, and endocardium of the left ventricle had a predisposition to calcium deposition. A supersaturation of the blood and tissue fluids with calcium salts is supposed to account for this condition which is found in diseases of bone, osteomalacia, and leukemic diseases. However, these calcium deposits are sometimes found when there is no accompanying disease of bone or blood. Harbitz¹ reports such a case in which both lungs were heavily infiltrated with calcium. Their combined weight was

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4,880 gm. Calcium is deposited in tissues where acids are given off, as in the lungs, kidneys, and gastric mucosa. The walls of the pulmonary arteries escape but the pulmonary veins do not because they carry blood that has lost much of its carbon dioxide. Calcium is also deposited more readily when its elimination by the kidneys, as in chronic nephritis, is interfered with. Recently we found calcium deposits in the lungs, and possibly gastric mucosa in two cases of chronic nephritis. One of them showed deposits in the kidney also.

CASE I. L. B. (history 57836, autopsy 9424), a colored woman of thirty-eight, was admitted on August 29, 1923, complaining of shortness of breath, and vomiting after meals. Her past history was negative. Physical examination showed a thin, poorly nourished individual. The upper part of the left lung was less resonant than the right, and there were many medium moist crackling râles at the left base. The heart was enlarged to the left, with a diastolic gallop and short blowing systolic murmur at the apex. The liver was enlarged. Pitting edema was present in both ankles. The blood pressure was: systolic 220, diastolic 160. The Wassermann test was negative. The blood urea was 5.6 gm. per litre. The urine showed a specific gravity of 1.017, very heavy trace of albumin, an occasional granular cast and red blood cell, and many clumps of white blood cells.

The patient died twenty-six days after admission with symptoms of chronic nephritis and uremia.

At autopsy the right lung was found to be everywhere adherent to the chest wall; the left lung was pushed to one side by the enlarged heart. Except for adhesions and edema, the right lung showed nothing unusual. The left lung was air-containing; the cut surface was grayish-red and frothy fluid exuded from it. At the base of the lower lobe was a firm, wedge-shaped, grayish-red area which had a gritty feel. This area measured about 5 x 4.5 cm. and had a rather porous appearance. It was a little lighter in color than the surrounding lung. On removing a section a small cheesy cast was found in a bronchiole leading to this solid area. The left lung weighed 400 gm., the right 550 gm.

The kidneys weighed 140 gm.; their capsules stripped with some difficulty; nothing unusual was made out otherwise.

Microscopic section of the mass in the left lung shows that the alveolar walls are thickened. Many of them are composed of a purple staining translucent crystalline material, very irregular in outline, suggesting calcium. There are many granules and blunt needle-like processes of the same material around these larger masses. Sometimes only the latter are found in the alveolar walls which, in these cases, have a spongy appearance. The walls of the blood vessels show the same changes; the lumina are restricted by an increase in connective tissue within the calcified wall. A large branch

of the pulmonary artery shows complete absence of calcium in the wall, whereas all the veins are affected more or less. Many of the alveoli are confluent, they are filled with loose connective tissue and fibrin for the most part. The walls of the bronchioles contain no calcium. A von Kossa stain verified the presence of calcium in the areas indicated.

About the middle of the gastric mucosa in several places the ducts are thin, appear rather granular, and take a bluish-red stain suggesting the presence of calcium, which the von Kossa stain does not verify.

The kidneys show evidence of chronic nephritis. There is a small infarct in the cortex of one. No calcium is seen.

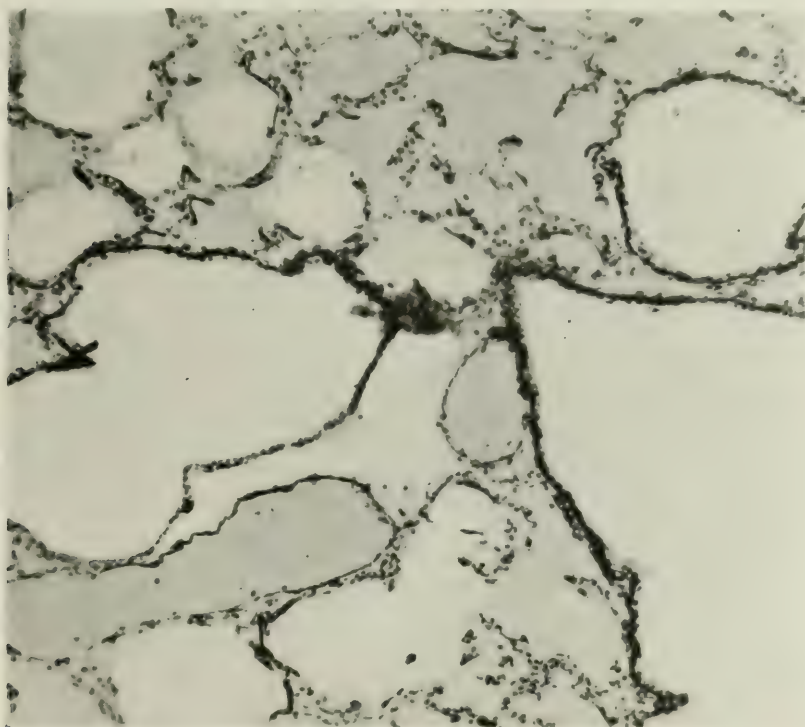


FIG. 1. Photomicrograph of lung of Mouse 101 on acid diet, showing calcium in the pulmonary veins, bronchioles and alveoli

CASE 2. I. O. (history 55400, autopsy 9443), a white woman of thirty-one, was admitted on a complaint of bilious attacks, headaches, swelling of legs and ankles, and palpitation, of eight years' duration. She had had pneumonia and pleurisy at twelve years of age. Physical examination showed a poorly nourished white woman with slight edema. The heart was enlarged, and the lungs clear except for a few moist râles at both bases. The urine showed a heavy trace of albumin, and an occasional hyaline and granular cast. Phthalein excretion was less than 10 per cent. The blood urea was 1.43 gm. per litre; it rose to 3.63 gm. per litre before death.

At autopsy the right lung was rather heavy, the pleura over the upper lobe covered with a thin fibrinous exudate; on section the lung showed edema

and in the upper lobe near the apex was a slightly elevated area of consolidation. The left lung showed edema but no consolidation.

Microscopic section of the right lung shows thickened alveolar walls which in places contain irregular reddish-blue staining crystalline deposits which suggest calcium. Some of the alveolar walls have a foamy appearance due to the presence of this material in the walls of the capillaries which are cut across. The walls of the pulmonary veins show a similar deposit in the media.

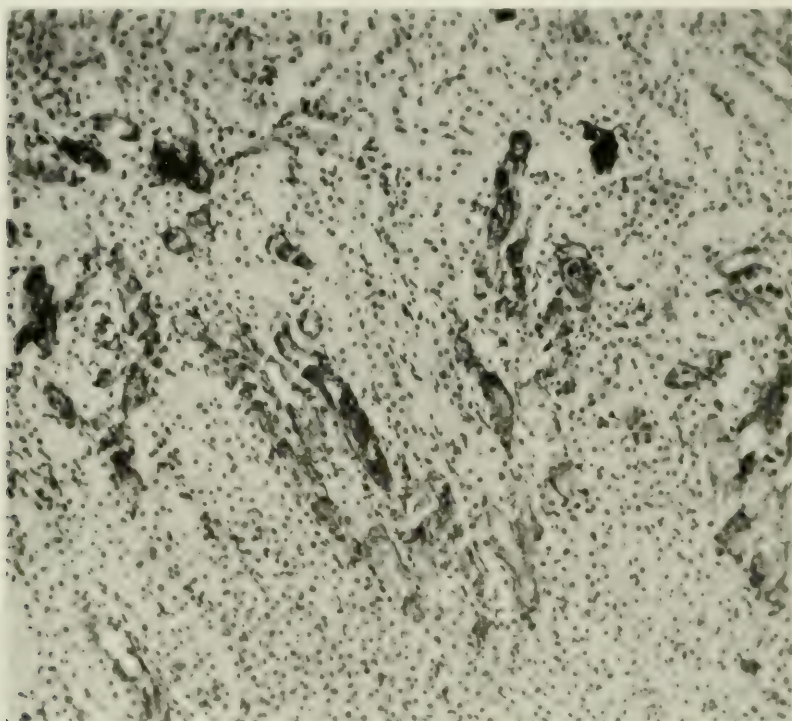


FIG. 2. Photomicrograph of kidney of Mouse 304 fed on alternating diet, showing calcium

About the middle of the glands of the gastric mucosa are numerous bluish-staining deposits which suggest calcium.

In one field in the kidney are three small deposits of calcium in the tubules.

The deposits in the lung and kidney give the reaction for calcium with the von Kossa stain; that in the stomach does not.

Rabl² was able to produce calcium deposits in mice experimentally. These deposits are similar to the so-called "calcium metastases" in man. Using the same diets we duplicated Rabl's experiment as closely as we could.

The control mice were fed bread, potatoes, and sometimes oats. The mice on the acid diet were fed:

Stock diet.....	20 gm.
Phosphoric acid.....	0.3 c.c.
Filter paper, q. s.	
Water, q. s. to make paste.	

The stock diet consisted of:

Dry milk (Dryco).....	10 parts
Sugar	10 parts
Tertiary calcium phosphate.....	1 part

The mice on the alkaline diet were fed:

Stock diet.....	10 gm.
Cooked potato.....	30 gm.
Saturated solution sodium acetate.....	3 c.c.

The mice on the alternating diet were fed first the acid diet, and then the alkaline diet, changing every third day.

The first experiment was done, using twenty mice. It was found that these mice were afflicted with mouse typhoid. The experiment was repeated, using twenty-five mice. One group of controls was added; they were fed in addition one gm. of calcium phosphate to forty gm. of control diet. The mice in the second experiment were much healthier and showed less calcium deposit than those in the first.

Of the seventeen controls on the regular diet, only one mouse showed any calcium, a small deposit in the tubules of one pyramid. Two mice fed on the alkaline diet also showed no calcium. Many necrotic areas were found in the spleens and livers of the mice in the first experiment; these invariably showed the deposition of calcium.

The sections were stained by the von Kossa silver nitrate method, which is the most satisfactory stain for calcium, and also with hematoxylin and eosin.

The following table shows the incidence of calcium in the lungs, stomach, and kidneys.

	Lungs	Kidneys	Stomach		Days
<i>Acid diet</i>					
Mouse No. 100.	++++	++	o	Died	5
101.	++++	++	+++	Died	9
102.	++	++	+++	Killed	12
103.	+	o	+	Killed	12
104.	+	++	o	Killed	8
105.	+	++	+	Killed	10
106.	++++	++	o	Killed	12
107.	o	+++	o	Killed	14
108.	o	++++	o	Killed	16
<i>Alkaline diet</i>					
201.	+	++	+++	Died	8
202.	++	+	o	Died	11
203.	+	+	o	Killed	12
204.	o	o	o	Killed	12
205.	+?	+	o	Killed	8
206.	o	++	o	Killed	10
207.	o	o	o	Killed	12
208.	o	o	o	Killed	14
<i>Alternating diet</i>					
300.	+?	++	o	Died	4
301.	o	++	+	Died	4
302.	++++	++++	+++	Died	8
303.	+++	+++	o	Died	8
304.	++	++++	o	Died	8
305.	++++	+	+	Died	11
306.	o	++++	o	Killed	8
307.	+	++++	+?	Killed	10
308.	o	+++	o	Killed	12
309.	o	++++	o	Killed	14
310.	+?	++++	+	Killed	16

In the lung, calcium is deposited along the alveolar septa in long, needle-like masses, also in smaller clumps. Sometimes only small granules were seen. In the pulmonary veins calcium lies just under the intima, in the bronchioles it is apparently along the basement membrane and in the bronchial cartilage. In the pulmonary arteries it is just beneath the intima. Only four cases of calcium deposit were found in the pulmonary arteries, of two mice on acid diet, and two on alternating diet. Ten mice showed calcium in the pulmonary veins.

Rabl found localized deposits of calcium in the elastic fibres of the alveoli and heavy deposits in the bronchi. The bronchial cartilage always showed marked deposits. In a single case were calcium thrombi seen in the lung capillaries of a mouse having

pneumonia. Rabl seldom found any calcium in the pulmonary veins which, when present, was located in the intima and media. He also found calcium deposited in the intima, media, and adventitia of the arteries. In our experiment we found calcium in one case beneath the intima of the aorta; only a few sections of aorta were made.

In the stomach we found only meagre deposits in the lower portion of the glands. In the mucosa and in the muscle single cells were seen in which calcium was deposited in the position and shape of the nucleus. Calcium is also found beneath the intima of the arteries and in the muscle in one place. The portion of the stomach lined by squamous epithelium contains no calcium.

Rabl found calcium mostly in the tunica propria, in capillaries of the serosa and muscularis, and seldom in the gland cells. There was one ulcer of the gastric mucosa following calcium deposit in the tunica propria.

We found the heaviest deposits of calcium in the kidneys in the zone between cortex and medulla. Deposits are seen in the epithelium of the tubules and in large masses in the lumina. Often other large deposits were found in cortex and pyramid. In the mice fed on the alternating diet, a yellowish zone about 1 mm. wide could be seen in the gross along the junction of cortex and medulla. Rabl likewise found calcium deposited near the junction of cortex and medulla, with single calcium casts in many places of the tubular system. In about one fourth of the cases calcium was deposited in the tunica propria, most noticeable in the cortex, not so great in the papillæ, and seldom in the rest of the medulla. There was never a great deposit in the epithelial cells of the kidney but calcium granules were present at all times.

In the heart we found calcium in only five cases, in only two cases were there any very large deposits which pushed the fibres aside. Calcium was found in the walls of a few coronary vessels and in one case only granules were seen in the fibres.

Rabl found calcium in the individual muscle cells in the beginning; later there were small calcium "clots" surrounded with

cells having sometimes a round and sometimes an oval nucleus. In the larger deposits the muscle fibres are pressed apart by the calcium masses. No foreign body giant cells were found.

In none of our cases were foreign body giant cells seen or any leucocytic reaction around the calcium deposits.

In Rabl's experiment seven mice fed on acid diet showed heavy deposits in the heart and kidneys, but none in the stomach, lungs, and vascular system. Rabl concludes that in animal experimentation, through feeding of acid and alkali with excess of calcium in the diet, one can imitate the picture of calcium metastases and calcification of arterial walls. He explains calcium metastases in the human by oversaturation of calcium combined with the disturbance of acid metabolism as a result of renal disease.

This is an interesting development and calls for further analysis of the factors controlling calcification.

References:

1. HARBITZ: *Arch. Int. Med.*, 1918, xxi, 139.
2. RABL: *Virchow's Arch. f. path. Anat.*, 1923, ccxlv, 542.
3. WELLS, H. G.: *Chemical Pathology*, Ed. 4, Philadelphia, W. B. Saunders Co., 1920, p. 442.

Discussion:

DR. MOSCHCOWITZ: I should like to ask whether you found any changes in the bone marrow.

DR. BUTLER: We did not examine the bones at all. I might add that we found no foreign body giant cells around these deposits, nor any leucocytic reaction around them.

DR. MOSCHCOWITZ: It is very remarkable that in pathological calcification the most common sites are the lungs, stomach, and the kidney, which bears out Dr. Butler's contention that there is a disturbance in the acid-base equilibrium.

DR. PAPPENHEIMER: It is difficult to interpret these results, because of their occurrence on acid and basic diets alone, or on alternating them. The method is promising because it makes it possible to approach the subject experimentally, and to induce calcification under controlled conditions. It should be a fairly easy matter to proceed with a further analysis of the problem, by carrying only one factor in the diet.

GENERAL STREPTOCOCCUS SEPSIS, ASSOCIATED
WITH SUPPURATIVE INFLAMMATION OF THE
THORACIC DUCT: REPORT OF A CASE *

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The thoracic duct is very seldom involved in an acute inflammatory process, though it undoubtedly transports infected material, especially in suppurative lesions of the peritoneal cavity and retroperitoneal tissues and lymph glands. The reaction of the duct is much the same as that of the blood vessels, namely, that the transportation of infected fluid does not necessarily mean the entire vessel is infected but that there is some point at which such infected material is being poured into it. The case to be reported here is one of the rare instances in which the duct has become acutely inflamed.

The subject of this report (L. K., aged seventeen, male, history 57209, autopsy 9396) was a private patient of Doctor George Draper, to whom I am indebted for the clinical history. While playing baseball, he injured himself, suffering an abrasion over the trochanteric region of the left thigh. A small abscess developed at the site of the abrasion, and this was incised twice. With the appearance of the abscess, the femoral glands became enlarged. Four days after the incision of the abscess, he began to have fever, with pain in the abdomen, severe backache, headache, nausea, and a "lame feeling all over." His temperature rose to 105°. Forty-eight hours after these generalized symptoms, *Streptococcus hemolyticus* was obtained in the blood culture. The following day the left ankle became red, and there was swelling over the right sternoclavicular region.

When admitted to the hospital, the physical examination revealed two small wounds of the left thigh, covered with crusts; the lymph nodes at the junction of the left internal saphenous and femoral veins were enlarged and tender. A soft systolic murmur, not transmitted, was heard at the apex of the heart. There were no petechiæ. The white blood count was 22,200, with polymorphonuclear leucocytes 91 per cent. The blood culture showed *Streptococcus hemolyticus*.

He rapidly became worse; his temperature varied from 101 to 105°, pulse 80 to 140. The heart action became irregular and the breath sounds were suppressed over the right chest posteriorly. He died two days after entrance into the hospital, fourteen days after injury.

* Presented April 10, 1924.

The postmortem examination showed swelling and injection of the bulbar conjunctiva of the left eye. The axillary and left inguinal glands were enlarged to palpation. Over the left greater trochanter were two small ulcerated areas, having sharply defined edges, their bases formed by the fascia lata. The underlying muscles were unaltered.

The peritoneal cavity contained 200 c.c. of thick, creamy yellow pus, most of which was in the pelvis. The serous surfaces of the intestine and the parietal peritoneum were injected and dull. Much of the small intestine lay in the pelvis, and the loops so situated were bound together by a fibrino-purulent exudate.

The glands in the left inguinal region and those along the left iliac vein and artery were greatly swollen, their capsules tense, and rolling backward on section. The cut surface of the glands was injected and not so translucent as usual. In contrast to these, the glands in the right inguinal region, and along the right iliac vessels, were much smaller, appearing normal on section.

As the glands along the left iliac artery and vein were followed upward, they became larger, and the glands on either side of the abdominal aorta were found to be enlarged and soft, and the tissues about them, edematous. These glands were injected, and hemorrhages were present in them. Between the superior and inferior mesenteric arteries the glands were extremely large, and in the neighboring areolar tissue were small accumulations of pus lying, apparently, within small vessels. The involved glands entirely encircled the aorta in this region. The glands in the posterior mediastinum were swollen but to a less extent than were the retroperitoneal glands.



FIG. 1. Suppurative inflammation of the thoracic duct

The thoracic duct was greatly distended, measuring in its lower part almost 1.5 cm. in circumference. It was filled with purulent material in which were flakes and masses of fibrin. The receptaculum chyli was distended with pus to a marked degree, and its walls were friable. The intima of the duct was covered with a purulent exudate; in its upper portion were small subintimal accumulations of pus (Fig. 1). Near the upper end the

lumen was completely filled with a fibrino-purulent mass. Above this plug the lumen of the duct, while containing pus, was less than 0.5 cm. in circumference. The wall of the entire duct was edematous. In the tissue about it were small channels filled with pus.

Other findings in the case were an acute splenic tumor, infarcts of the left lung, suppurative pleurisy, right, and suppurative arthritis of the sterno-clavicular joints.

On histological examination, the peripheral sinuses of the left iliac glands were found to contain many polymorphonuclear leucocytes and large mononuclear phagocytes. These glands were edematous and the vessels within them dilated. In contrast to them, the glands along the right iliac vessels were not involved; their sinuses were quite narrow, and they did not contain any polymorphonuclear leucocytes. In the retroperitoneal glands the changes were quite similar to those described in the left iliac glands. In the fat about the retroperitoneal glands were many greatly dilated lymph channels containing few cells.

Sections from various levels of the thoracic duct showed marked edema of its wall, with an acute inflammatory exudate upon the inner surface. In the exudate were great colonies of Gram-positive streptococci (Fig. 2).

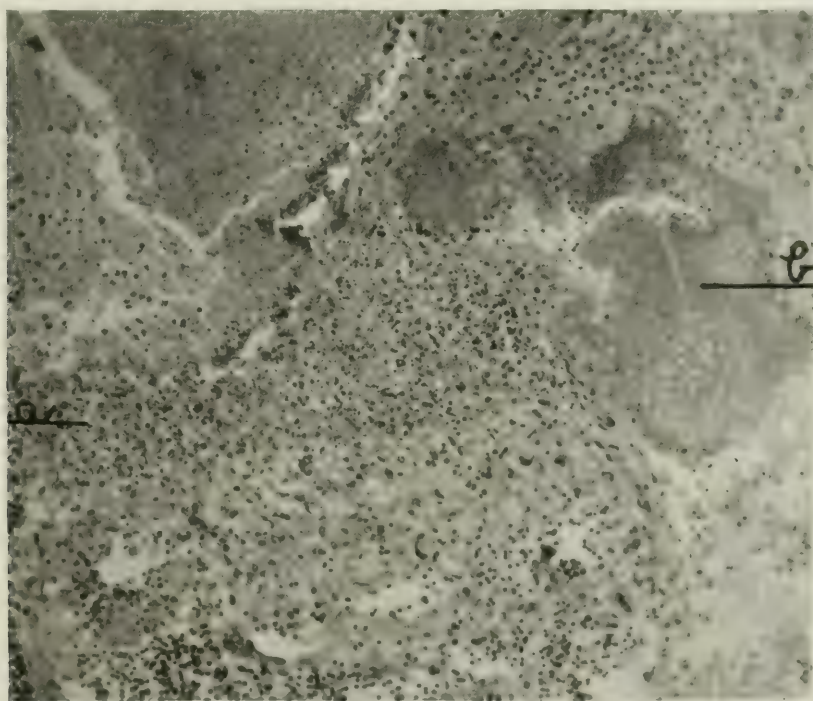


FIG. 2. Suppurative inflammation of the thoracic duct. *a*, wall of duct.
b, exudate containing masses of bacteria

Similar organisms were found in the peripheral sinuses of the retroperitoneal and left iliac glands.

The inflammatory reaction extended through the wall of the duct into

the surrounding tissues, where there were hemorrhages, edema, and polymorphonuclear leucocytes, as well as small mononuclear wandering cells. The lymph channels around the duct were hugely distended with an acute inflammatory exudate, and contained many streptococci. Sections through the upper end of the duct showed the lumen to be completely filled with fibrin and fragmented polymorphonuclear leucocytes.

The case is obviously one of infection spreading by way of the lymphatics to the thoracic duct, and thence to the blood stream. Careful search did not reveal any infected or thrombosed blood vessels near the primary focus of infection, and it has been our experience that such involved vessels are easily demonstrable.

There are on record few instances of acute infection of the thoracic duct. P. Pappenheimer¹ was able to collect from the literature only ten cases, and to these he added two others. He did not include, however, the cases reported by Warthin² and DeForest.³ In addition to the case reported here, there are fourteen other cases on record.

I wish to express my thanks to Mr. Alfred Feinberg for the drawing.

References:

1. P. PAPPENHEIMER: *Virchow's Arch. f. path. Anat.*, 1921, CCXXXI, 274.
2. WARTHIN: *Osler and McCrae*, 1908, iv, 582.
3. DEFOREST: *N. Y. State Journal of Medicine*, 1907, vii, 349.

SOME PATHOLOGICAL CONDITIONS ASSOCIATED WITH CONGENITAL DEFECTS OF THE KIDNEY *

HALSEY J. BAGG, PH.D.

My remarks this evening will be divided into four main groups: first, the nature of the experimental strains of animals in which the congenital defects of the kidney were found, and a brief description of certain structural defects associated with the kidney abnormalities; second, the etiology of the associated de-

* Presented May 8, 1924.

fects; third, a description of the kidney abnormalities; and fourth, a consideration of the underlying factors possibly associated with the production of the kidney defects.

Our procedure was as follows: A single group of laboratory animals was divided by chance into two groups; one was x-rayed with a light dose of unfiltered x-rays. The other group was kept as a control. The x-rayed group was inbred for several generations, as was the control group. In the third generation of the x-rayed group certain animals were found with characteristic defects of the eye. By careful selection of animals showing this defect and continuing through several generations, we have now been able to obtain a strain of animals which shows this characteristic defect in a very high proportion of cases. In the tenth generation we have various litters which show these changes in 100 per cent. of their offspring. Over 3,000 abnormal animals have been examined, and 2,000 control animals, and we have never found in the control animals any such hereditary defects. Only one treatment was given. The inheritance of this defect has been very carefully worked out, and we can say that the defect behaves as a Mendelian recessive. We do not believe that these are examples of the inheritance of so-called acquired characteristics. We are inclined to believe that the defects are due more likely to the direct action of the physical agent upon the germ plasm.

The following structural abnormalities have been associated with the abnormalities of the kidney: eye defects, including cataract, obliteration of the eyelids, due either to early atrophy or arrested development, atrophy of the entire eyeball; also club-feet; syndactylism and polydactylism. In each of the three groups we have a considerable number of representative individuals.

Concerning the etiology of the associated defects, they are apparently closely connected with blood vascular extravasations occurring in early embryonic life. These are commonly found in the head region and also in the region of the foot. We believe they produce arrests in development. It would seem that

the rate of development of a localized portion of the embryo was interfered with, and as a result, the animal would later show characteristic morphological changes.

The following is a brief description of the various types of kidney abnormalities:

1. The kidneys are unequal in size, one being apparently normal, and the other reduced one quarter to one third in size. These cases are fairly rare. Six were found in a group of 400 autopsies.

2. One case of congenital cystic kidney, in which case there was an abnormal eye on the same side of the body.

3. Three cases of hydronephrosis, also associated with eye defects.

4. Almost, but not quite complete obliteration of one kidney; the other kidney being hypertrophied. There were six such cases.

5. One kidney completely missing, and the other hypertrophied in each instance. There were over 100 cases in this group. I have reason to believe that in a group of laboratory animals the absence of one kidney is found about once in several thousand times. The absence of one kidney is usually associated with blindness or abnormalities of the foot, or both. Lack of one kidney was found with equal frequency on the right and left side of the body.

6. Both kidneys missing at birth. We have so far twenty cases. This condition is also associated with eye defects, and these animals usually have had for parents animals with the unilateral kidney condition. Animals with congenital absence of both kidneys are born alive in many instances. Death usually occurs within twenty-four hours after birth.

At the present time I have not sufficient data to venture an explanation concerning the etiology of the kidney abnormalities. The conditions *in utero* are obscure, and need considerable future work. However, in four or five instances hemorrhages were found in the region of one or both kidneys, suggesting the possibility that the eye, foot, and kidney abnormalities were all due to early arrest of embryonic development, associated with blood vascular disturbance.

Discussion:

DR. SEECOF: I was especially interested in the adrenals in the side where the kidneys were missing. In human autopsies I have seen one such instance, and in the literature changes in the suprarenals are described. The most consistent change is that it does not take its involutions and convolutions like the normal one would. It would be interesting to see absence of the kidneys with cystic and normal suprarenals.

DR. BAGG: The adrenals were apparently normal in my animals with abnormal kidneys.

FURTHER REPORT ON ENDOTHELIAL MYELOMA
OF BONE *

JAMES EWING, M.D.

About the year 1920 I reported to this Society evidence indicating that in the group of bone tumors commonly called round cell sarcoma there is one which is probably a specific neoplastic disease of bone or bone marrow, and which shows histological characteristics which at that time led me to suggest the designation "endothelioma," and since it was mainly a tumor of the bone marrow, "endothelial myeloma." Experience with this group of cases since that time has included observations on about thirty more cases, most of which seem to belong to the same group, and I have this evening to present conclusions which seem justified regarding the clinical characters, course, gross anatomy, and structure of this group.

The clinical characters impress me as highly specific. A large proportion of the cases have occurred in young subjects, a considerable number at the age of fourteen years. A few cases have been observed much later, and some a little earlier. The disease begins with symptoms which recall osteomyelitis, and that diagnosis has almost constantly been made at the first attack of the febrile disturbance. The first attack is usually recovered from in a few days or a week or two, and the patient goes along for several weeks before another attack occurs. Then the attacks are repeated at shortening intervals, and are more severe, and soon the symptoms point to a persistent disturbance in some

* Presented May 8, 1924.

one bone. From that time on the picture is dominated by swelling and tumefaction of the bone which is chiefly affected. A characteristic feature also is the fever which usually occurs with these cases. It is pretty high in some instances, in one or two cases suggesting typhoid fever. The tumefactions are peculiar. They arise rather suddenly with a great deal of hyperemia and inflammatory disturbance, and they are apt to subside for a period. With each succeeding attack the subsidence is less marked, and eventually there is a persistent tumor. Eventually the patients die with multiple tumors, mostly in the bones of the skull, the extremities, and occasionally in the spine and ribs. Pulmonary metastases also occur. The regional lymph nodes may be involved. These seem to be rather distinct clinical features which strongly indicate the probability that the disease is not to be confused with any other form of bone sarcoma.

The gross anatomy is also characteristic. The disease is apt to affect the small bones of the extremities. I have seen two in the femur, one in the humerus, several in the tibia, the majority in the bones of the foot and hand, the ulna, clavicle, ribs, pelvis, and frequently in the skull. It affects the shafts of the bones, and not the ends, and one very striking feature is the wide involvement of the shaft, thus differing from osteogenic sarcoma. The tumors permeate through the periosteum and widen the shaft, so that a considerable tumor develops in the soft parts. No bone formation has occurred in any instance, either early or late.

The histological picture is the most difficult problem, and it was with considerable hesitation that I ventured to suggest the endothelial nature of this tumor four years ago. However, the observations in recent cases have at least not succeeded in displacing that interpretation from my mind. I still feel that they are to be assigned to some endothelial category, but it may be that the interpretation of "endothelium" may have to be widened to include this group. I do not think they arise from blood or vascular endothelium. They may possibly arise from perivascular lymphatic endothelium. The structure must show distinct

endothelial features in the cells before one should venture to make any diagnosis of endothelioma. The cells occur in sheets without any intervening material. They are usually small. The nuclei are small and vesicular. The cells often enclose blood sinuses, small or large, in which intact and apparently circulating blood is found. When these features are present I am willing to make a diagnosis of endothelioma. They are best demonstrated after Zenker fixation.

One of the features which impressed me early and was the main incentive to separate these tumors from osteogenic sarcoma was the reaction to radiation. These tumors melt down under heavy radiation, and I was at first hopeful that this regression would be permanent. In a few cases it appears to have been permanent, but I regret to report that the tumors generally recur. There is a residuum left from which the tumors in the majority of instances recur, after which they are more refractory to radiation, and a great majority of these cases have died from recurrence of the primary tumor and from extensions to other parts of the body. There are about twenty cases in the Codman Registry in which this diagnosis has been made by my colleagues, and while it is somewhat gratifying to find they are inclined to make this diagnosis, perhaps they are a little free in assigning cases of undetermined origin to this endothelial group. I am unwilling to accept many of these diagnoses, made on tumors which do not show endothelial characters, and in which the clinical history and gross anatomy are not typical. If the existence of this group of tumors is to be demonstrated, one must not include in it the small spindle cell or almost rounded cell type of undifferentiated osteogenic sarcoma, which is of osteoblastic origin. The relation to plasma cell myeloma remains an unsettled question.

Another matter of considerable importance is the question of the manner of dissemination of the disease. Nearly all the cases have died with multiple tumors of bones. In the types of endothelioma of bone previously described, the majority have been multiple, and there are some notable cases in the literature in which nearly every bone in the body was the seat of a local



FIG. 1. Vertical section of tibia in diffuse endothelial myeloma. Three years after radiation. Note fibrous mass of original extraperiosteal tumor, diffuse tumor growth in marrow, and perforation of shaft by actively growing tumor above.

tumor process, undoubtedly of endothelial origin. These were all alveolar, cystic, or angioendotheliomas. It is very difficult to determine whether the multiple tumors which are found, as indicated by clinical signs and radiographs, are metastases or multiple primary tumors. I have been unable to reach any conclusion, but the very extensive distribution of tumors in the later stages, and the comparative integrity of the other organs lead me to think that the dissemination of the disease is mainly from multiple primary tumors developing throughout the bony system. We have no autopsies on this group of cases. Bence-Jones body was not demonstrated in a single case. The question as to whether these are metastases or multiple tumors is of much importance in regard to the management of the cases. If they are multiple tumors there is little object in amputating. If they are metastases, there is every reason to amputate early or attack the main lesion aggressively. The history of the treatment of the cases shows that in spite of amputation the great majority develop multiple tumors.

I have to report on one case mentioned here four years ago, a tumor of the tibia, which had given a primary response to radiation. This was in a young man sixteen years old at that time. The tumor was apparently controlled for about three years by external radiation, and then recurred and required amputation. It is interesting to see how the original tumor had been converted into a large mass of fibrous tissue in the bone marrow and in the periosteum, but outlying portions near the epiphyseal line had broken through the periosteum and called for amputation. This boy is apparently free from secondary growths. Fig. 1 shows the gross appearance of the tibia in this case, three years after the beginning of treatment by radium, and about four years after the onset of symptoms. In all about 50,000 millicurie hours of radium, in pack, brass filtration, 6 cm. from the skin, were used. The skin was blistered, and no more radiation could be used.

Vertical section through the tibia shows that the extraperiosteal tumor was reduced to a fusiform mass of dense hyaline connective tissue in which were numerous islands of stainable tumor cells. Throughout the bone marrow of almost the entire bone there is much fibrous connective tissue, areas of complete hyalinization, but many foci of tumor cells. The shaft of the bone is markedly thickened as a result of chronic radiation osteitis. Near the upper epiphyseal line, especially on the inner aspect, there are small areas of cellular tumor tissue, which at one point had perforated the shaft and was invading the muscle tissue. There was nowhere any evidence of deposit of osteoid tissue or bone by the tumor. The structure of the growing portions of the

tumor was that of typical endothelioma, with sheets of polyhedral cells, clear cytoplasm, and absence of intercellular material.

There are one or two other cases in the Registry which have been treated by local excision and radiation and which have done well. We have one case, a tumor of the spine, apparently well three years after full radiation on the spine, having recovered from paraplegia. All the other cases show signs of recurrence or are dead.

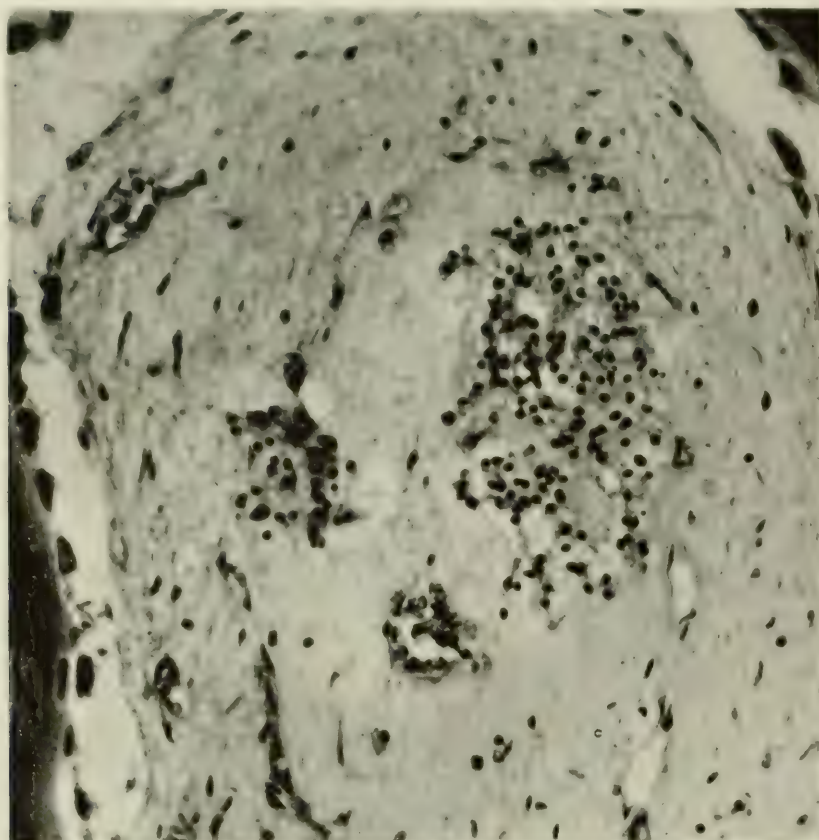


FIG. 2. Isolated groups of tumor cells lying in perivascular lymphatics, and probably originating there, on edge of diffuse endothelial myeloma of tibia.

The origin of the tumor is, however, what interests one most, and I have one piece of evidence indicating that the tumor possibly arises from perivascular endothelium. It seems to be important evidence, because while some of my colleagues think the tumor is an undifferentiated osteoblastic sarcoma, they have not given any definite evidence in support of that view.

Figs. 2, 3, and 4 are taken from the outskirts of an early case of diffuse endothelioma of the tibia in a young boy. The case is No. 160 in the Codman Registry.

The gross lesion showed a very early tumor process partially replacing the marrow tissues over a short upper segment. It had not yet definitely perforated the bone, and its neoplastic character was not obvious in the gross. Yet sections showed the usual appearance of diffuse endothelioma in the center of the area. Beyond this area the marrow was only slightly altered and pre-

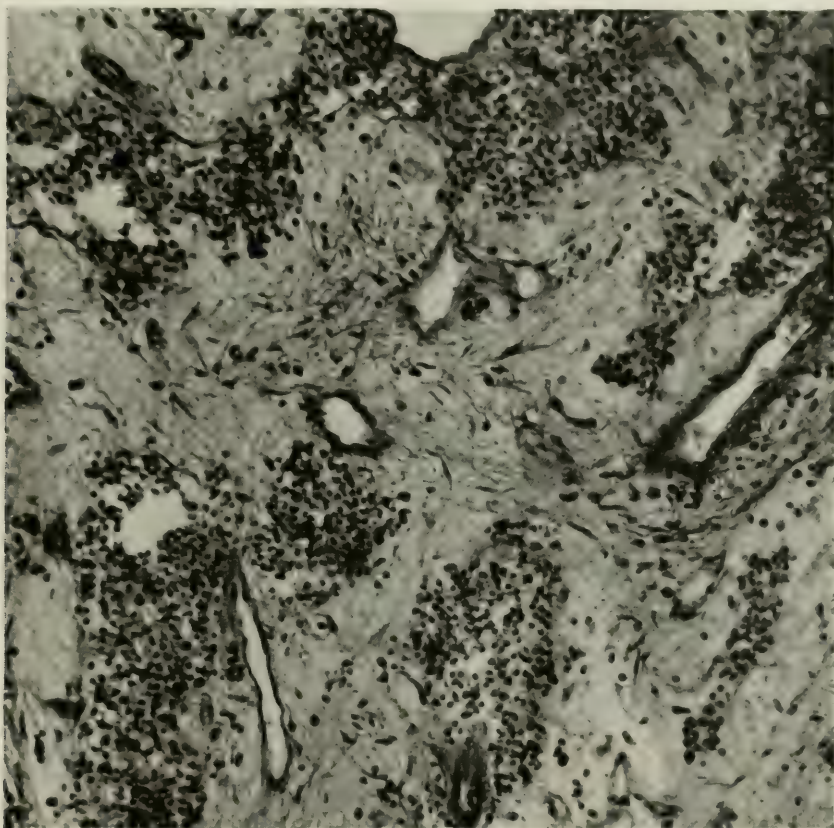


FIG. 3. High power view of more solid growth of diffuse endothelial myeloma of bone

sented the structure shown in the figures. The earliest lesion consists of the appearance of small numbers of tumor cells about the blood sinuses. Even in the sections it is difficult to determine the nature or source of these cells. They seem to me to lie in the perivascular lymph spaces and to be derived from the perivascular endothelium. The alternative hypothesis is that they are extensions along the lymphatics from the main tumor. Nearer the main tumor they become gradually more numerous and finally diffuse. It is possible that they reveal the mode of origin of the tumor. The patient is reported to have died several months later with multiple tumors; total duration, fourteen months.

The results of the studies of these cases impress me more and more with the fact that the pathology of bone and bone

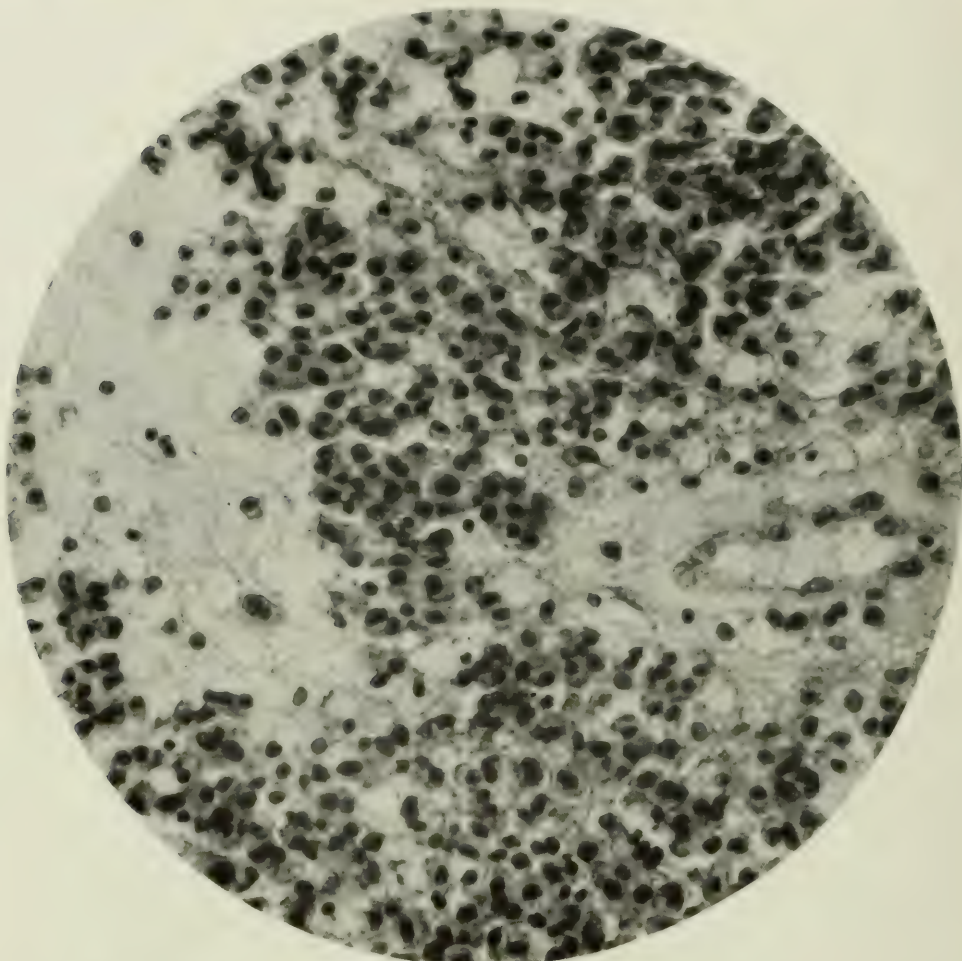


FIG. 4. Numerous isolated groups of tumor cells distending perivascular spaces and infiltrating fibrosed marrow tissue

marrow is largely unexplored territory. We have not the slightest conception of how or why the tumors develop. The febrile period in the beginning strongly suggests that an infectious agent may be connected with it, as it is probably connected with lymphosarcoma. I still remain of the opinion that this is a specific disease of bone. With a lack of evidence of some other origin and nature of the tumor it seems best to retain the designation of endothelial myeloma. Direct radiation alone will probably not control the majority of these tumors. It appears to have controlled some. Some appear to be controlled by local excision and

local radiation. At present one may recommend repeated radiation, await the outcome, and at a point of definite recurrence, excise or amputate. The causation of the tumor is quite obscure. It suggests a relation to some infectious process in the body, similar to that found in some types of lymphosarcoma. The histogenesis is still undetermined. It is too early to give a satisfactory statistical report on the whole series of cases observed.

MULTIPLE TRAUMATIC CEREBRAL HEMORRHAGES *

CHARLES S. B. CASSASA, M.D.

My purpose in presenting this particular type of brain injury, multiple traumatic cerebral hemorrhages, is threefold:

1. It is a relatively rare finding at autopsy on cases that have received a head injury.
2. It indicates the necessity of conservative treatment.
3. It may possibly explain the pathology and mechanism of the many so-called cases of concussion of the brain.

During my ten years of close association with Dr. Otto H. Schultze and Dr. Charles Norris, five cases were encountered among the many thousand autopsies on persons dying as a result of trauma to the head.

The salient points in the clinical histories were as follows: All were males. Their ages varied from twelve years to forty-one years. All had a history of a head injury without a laceration of the scalp. Three were operated upon, the pre-operative diagnosis being epidural hemorrhage in two, cerebral edema in the other. Three were momentarily unconscious at the time of injury, then there followed a lucid interval, varying from three to twenty-four hours, followed by a period of marked irritability and increased deep reflexes, then unconsciousness.

In two cases the early history was not ascertainable; the patients were admitted to the hospital in a semi-conscious condition,

* Presented May 8, 1924.

very irritable, and deep reflexes increased, sensitive to light and sound. In all cases pupils were equal and contracted and reacted to light. Lumbar puncture in three cases showed clear cerebrospinal fluid, one recorded as being under increased pressure. Two had a fracture of one or other extremity.

All were autopsied within twenty-four hours after death. Examination in all cases failed to reveal either fracture of the vault or the base of the skull. The meninges were intact. The cerebrospinal fluid was clear. The brain showed normal conformation of convolutions and sulci without any cortical laceration or contusion.

Gross section showed very many scattered, minute hemorrhages (Fig. 1).

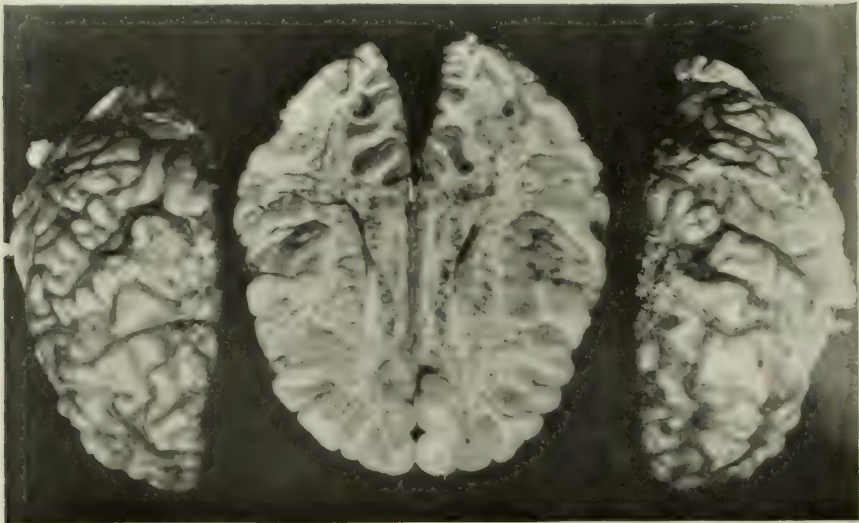


FIG. 1. Photograph of brain showing many minute hemorrhages

Microscopical examination of the areas of hemorrhages showed some of the hemorrhages limited to the perivascular lymph spaces; others were within the immediate adjoining brain substance (Fig. 2).

Mechanism: A brain fixed by embalming before its removal from the body shows a network of fine fibrils connecting the external wall of the blood vessel with the surrounding brain tissue across the perivascular lymph space.

Sudden overfilling of the perivascular lymph space with cerebrospinal fluid conceivably could produce a laceration of a vessel by the tearing of its wall in the neighborhood of such a fibrillar attachment. Otherwise, without such an attachment,

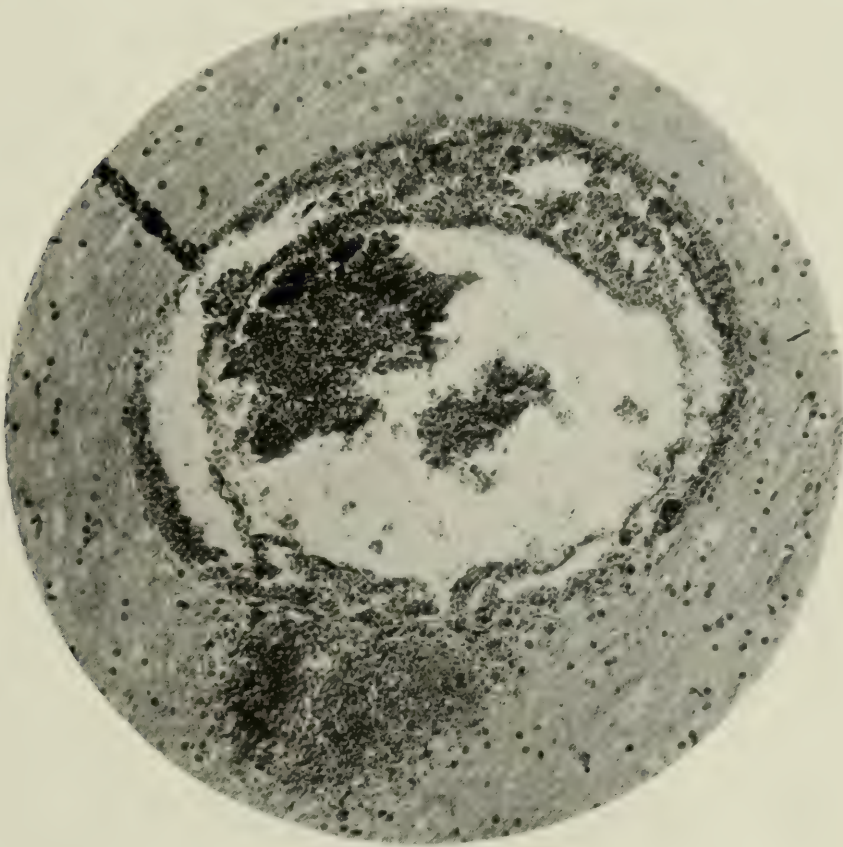


FIG. 2. Shows circular outline of a vessel with single endothelial wall, surrounded by hemorrhage into perivascular lymph sheath and into adjoining brain substance.

the laceration of a vessel surrounded by fluid could not be produced by any pressure exerted through that fluid which would only tend to compress the vessel but not lacerate it. For the purpose of making this physical condition clear, I have brought a slide showing a normal anatomical connection of vessel with the wall of the perivascular lymph space (Fig. 3). Such an increase of cerebrospinal fluid in the perivascular lymph space could be caused by the cerebrospinal fluid from the surface of the brain being driven into it by the pressure exerted in the change

of shape of the skull—the result of a blow or fall. This change of shape under an area of violence is in the direction of flattening and diminution of space for the cerebrospinal fluid in that area. This fluid must find its way out of that area through the various sulci of the brain and in connection therewith such fluid as can-

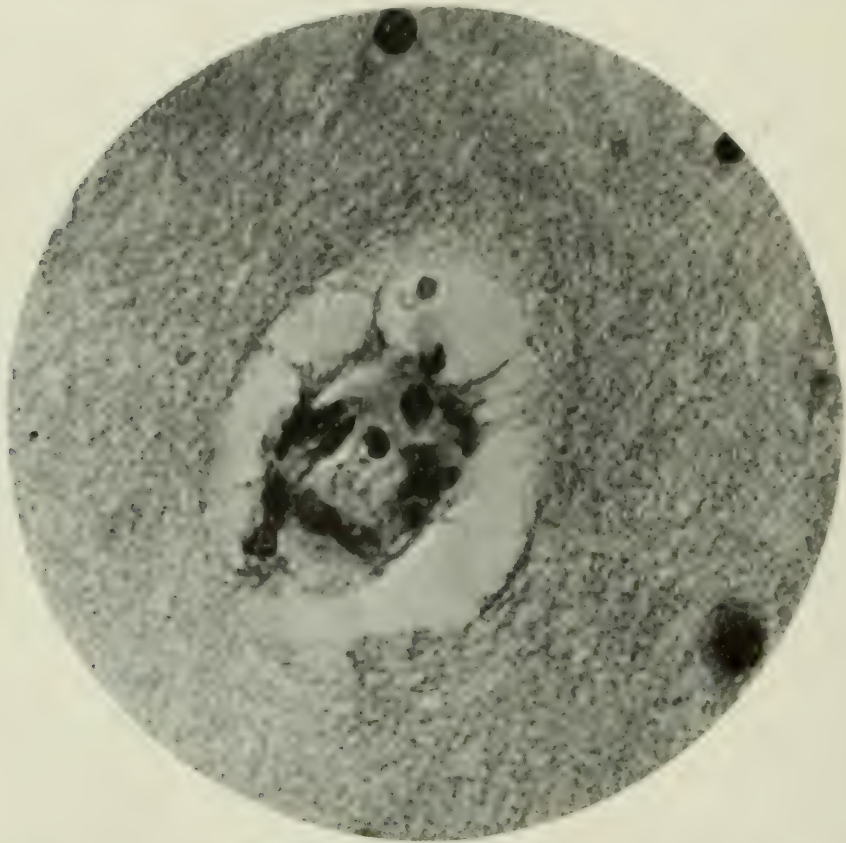


FIG. 3. Cross section of normal vessel to show fine fibrillar attachments to outer wall of perivascular lymph sheath

not find its way through these channels must find a way into the perivascular lymph spaces in the reverse direction of the normal flow of the cerebrospinal fluid in these channels.

May not this mechanism afford a simple physical explanation for the cause of cerebral concussion, instead of the vague explanation of shock, disturbance of equilibrium, *commotio cerebri*, and so forth?

By the injection experiments of Weed, the perivascular lymph sheath has been directly demonstrated to be connected with the

finest capillary lymph spaces about the cerebral ganglion cells. Sudden physical distension of these spaces by cerebrospinal fluid presents a condition of direct physical change associated with the infliction of the external injury, whether accompanied by fracture of the skull or not. It is conceivable that no other injury may be associated therewith and a complete recovery from this effect may shortly occur.

With the occurrence of hemorrhages, however, by the mechanism which I have here endeavored to explain, it is apparent that a more permanent condition of injury may result, depending upon their number and extent. Many cases of so-called prolonged concussion of the brain are in reality cases of this description. Many so-called sequelæ of concussion may thus be explained.

I desire to acknowledge my indebtedness to Dr. Otto H. Schultze for the microscopical slides (Figs. 2 and 3), and for the explanation of the mechanism of this injury and its relation to a mechanical explanation of the problem of concussion.

Discussion:

DR. EWING: I should like to ask how you account for that interval of rationality with the subsequent onset of unconsciousness.

DR. CASSASA: In pure concussion one often gets momentary stunning or unconsciousness. Then if the patients subsequently become conscious they remain conscious. Here I think the cerebrospinal fluid is driven into the perivascular lymph spaces and the primary shock transmitted to the ganglion cells. If in addition very many minute hemorrhages occur, the patient may become unconscious for a longer time and then regain consciousness. Compare this with the patient with cortical brain laceration. He will often be brought to the hospital unconscious, with a bloody spinal fluid. In the next hour or two he may answer questions and look as though he was going to get well. Upon going back to the ward you find him unconscious. What occurred was a primary concussion with a small amount of cortical hemorrhage which kept him unconscious for a while, but he stopped bleeding and then bleeding recurred and his secondary unconsciousness was due to a secondary hemorrhage or possibly to the additional reaction about the initial hemorrhage. May not the same condition, namely, recurrence of hemorrhage, or the reaction to the initial hemorrhage, occur in these cases which have a large number of small hemorrhages as it does in cases with larger lacerations?

DR. EWING: How are you going to distinguish the cases for the surgeon?

DR. CASSASA: We divide the head injuries with brain lesions into three

types. First, those with epidural clot. I have never seen a case that did not have a dilated pupil on the same side as the clot, whether it be an anterior meningeal, a middle or a posterior meningeal lesion. They all have clear fluid, provided they have no other injury. Their symptoms will usually be unilateral. Secondly; the five cases recorded have bilateral irritability, spasticity and equal pupils. Since the aggregate of these hemorrhages does not make a large clot, their blood pressure will not be high and will not go as high as cases with a large clot, as in an epidural hemorrhage and cases of cortical laceration. Although I have read that the cerebrospinal fluid was recorded as being under pressure in one case, this was not a personal observation. I think that the pressure of the cerebrospinal fluid as an indication for operation is not dependable. It has been shown that the cerebrospinal pressure increases with pain and excitability. The third type of cases is that associated with lacerations. The lacerations are cortical and since they are cortical they contaminate the cerebrospinal fluid and the lumbar tap will be contaminated with blood. The same is true of the depressed fractures with laceration of the brain immediately beneath the depressed area.

PRIMARY SPLENIC HODGKIN'S DISEASE *

ELISE S. L'ESPERANCE, M.D.

The purpose of this communication is to emphasize the existence of a form of Hodgkin's disease, predominant in the spleen with little or no involvement of lymph nodes associated with recurring attacks of fever.

The earliest case of pyrexial Hodgkin's disease was described with great accuracy by Murchison in 1870. The outstanding features of his case were an enormously enlarged spleen, recurrent fever and progressive enlargement of nodes. Pel in 1885 added three cases to the literature under the title pseudoleukemia. This was followed in 1887 by a detailed report from Ebstein of a new infectious disease. His observations extended over 211 days, in which time there were nine attacks of pyrexia with splenomegaly and progressive enlargement of nodes. From time to time isolated cases of this peculiar form of Hodgkin's disease have been reported, usually with indefinite pathological findings, and many therefore are of doubtful morphology. In 1909 Symmers reported a case in a girl eighteen years old. This case

* Presented May 8, 1924.

at operation for splenectomy showed no lymph node involvement. Unfortunately, a necropsy was not obtainable. Still this case appears to be the most authentic one predominantly splenic so far reported. Wade in 1913 added a very similar case to the literature, but this also was without autopsy findings. Mellon's and Linder's cases of so-called Pel-Ebstein disease both were associated with extensive superficial node enlargement. It must be noted that with the exception of the case reported by Symmers and possibly Wade's case, all the others combined extensive lymph node hyperplasia with splenomegaly and pyrexia. Therefore, the question may be raised as to whether there is a primary splenic type of Hodgkin's disease. This is the justification for the detailed report of the following case.

C. F., an American, forty-seven years old, was admitted to the Harlem Hospital complaining of abdominal pain, vomiting and fever. His history reveals the fact that he had had recurring attacks of this kind with jaundice for the past five months. The paroxysms usually lasted about six days, with apparently complete recovery in the interim. Three months ago, in what appears to be his third recurrence, he was operated on for supposed gastric ulcer. At operation an immensely enlarged spleen and liver were found, studded with white nodules. A diagnosis of miliary tuberculosis was made and the abdomen closed. He remained in fairly good condition for about six weeks after this operation. He then developed three more paroxysms at intervals of about three weeks. In each of these attacks the characteristic symptoms were manifested. He became extremely emaciated with profound anemia and died in the last seizure.

In all he had seven definite pyrexial periods extending over about six months. All these recurrences were characterized by abdominal pain, vomiting, irregular fever (101° to 105°), gradually increasing asthenia, jaundice and anemia. The blood picture was that of a mild leukopenia and secondary anemia.

Physical examination showed no palpable superficial nodes. The abdomen was distended, and there was marked rigidity and tenderness during the acute phase. This disappeared in the quiescent intervals. The spleen was found to extend to the spine of the ilium, and the liver was palpable four inches below the costal margin. With each recurrence the spleen appeared to increase in size, becoming smaller in the quiescent stage.

The autopsy performed ten hours after death showed an extremely emaciated male adult with intensely jaundiced skin. The visible mucous membranes were pale. There were no palpable nodes in cervical, axillary, inguinal or supraclavicular regions. The abdomen was prominent, especially on the left side, with resulting ventral hernia. On opening the abdomen the spleen occupied the entire left side, extending downward to the ilium and to the umbili-

cus in the midline. It measured 25 cm. in length, 12 cm. in cross diameter, and 8 cm. in thickness. The surface was irregular, roughened and thickly studded with myriads of yellowish-white, small, isolated, circumscribed nodules, varying in size from that of a pinhead to a split pea. There was no tendency toward fusion of these areas, each one remaining separate and distinct. On cross section the parenchyma appeared thickly beset with these small foci, leaving only scattered strands of splenic pulp intensely congested, suggesting a deep red framework strung with firm white beads. There was no gross evidence of necrosis or softening, and the consistence was firm but not hard (Fig. 1).



FIG. 1. Gross appearance of spleen

The liver was enlarged; the surface pale, and revealed numerous isolated white foci similar to those encountered in the spleen. The retroperitoneal nodes were just palpable. There was one enlarged calcific mesenteric node measuring $2 \times 1.5 \times 1.5$ cm. The other organs presented no noteworthy change.

Microscopic examination of the spleen revealed congested pulp surrounding large cellular islands, irregular in outline, their borders marked by groups of large polyhedral cells, with single large deep staining nuclei and clear cytoplasm. The larger areas were composed of many lymphocytes with fine anastomosing strands of connective tissue. Necrosis appeared in the large areas with a peculiar concentric arrangement of large endothelial cells which by the concentric form suggested early tubercles or thrombosed vessels. In some of the smaller foci a definite vessel wall could be made out with actively proliferating endothelial cells and large mononuclear cells resembling myelocytes. The location of these cells pointed to their derivation from lining cells of the sinuses. The nuclei showed abortive mitosis which resulted in fragmentation. Many large multilobed giant cells were present with a few plasma cells. There was conspicuous absence of eosinophile cells although there were scattered hemorrhages (Fig. 2).

In the liver the cellular areas were more isolated and their relation to the surrounding parenchyma clearer. They appeared as well circumscribed foci surrounded by compressed liver cells, dilated capillaries and occasional

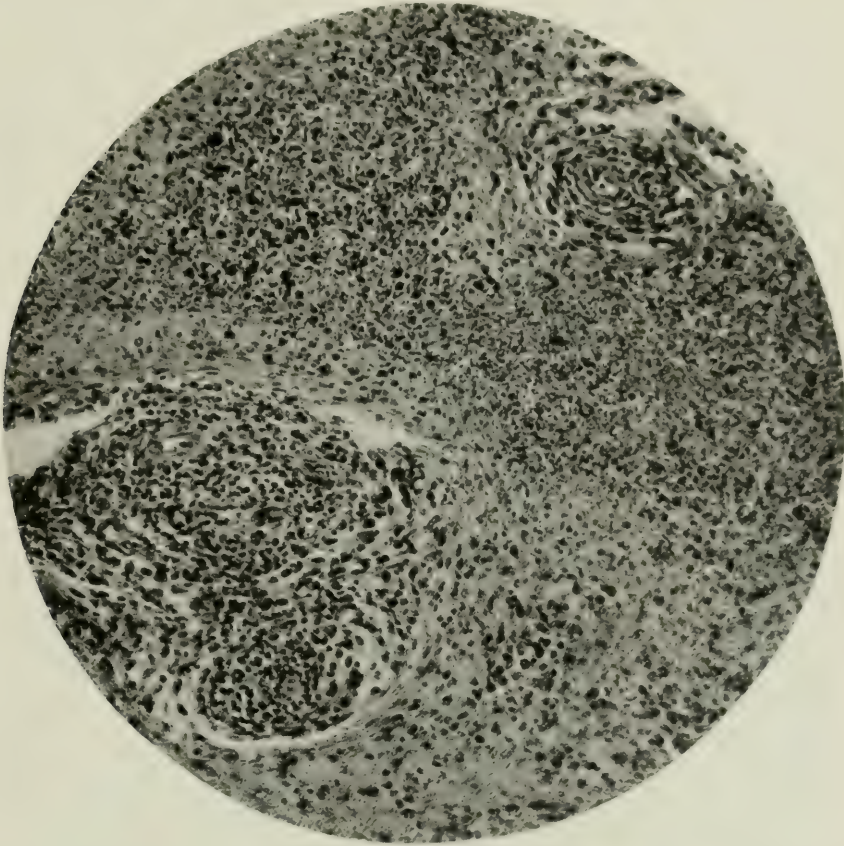


FIG. 2. Focal areas in spleen, one suggesting development around a small vessel

hemorrhages. They varied in size, the smaller ones suggesting tubercle granulum with vessels filled with proliferating endothelial cells and few giant cells. Then there were larger zones in which an entire liver lobule was replaced by hyperchromatic polyhedral cells, lymphocytes and giant cells and small areas of necrosis. These were of sufficient dimensions and of such cell characters with active mitosis as to simulate a neoplasm. The portal canals for the most part have remained immune and with the exception of a mild productive inflammation appeared quite unchanged (Figs. 3 and 4).

In the retroperitoneal nodes the capsule was uninvaded and consisted of rather dense hyaline connective tissue, and hyaline strands traversed the node in all directions, dividing it into segments. Each of these zones was composed of large mononuclear cells with irregularly shaped nuclei, giant cells and few lymphocytes. Islands of lymphocytes could be identified just beneath the capsule and along the hyaline strands.

In considering this case from the standpoint of the clinical history, one is impressed with the close resemblance to the disease described by Murchison, Pel and Ebstein, and generally recognized as Pel-Ebstein's type of Hodgkin's disease. The remittent character of the fever, with complete regression of symptoms in the intervals, the gradually increasing asthenia, anemia, jaundice and the progressive enlargement of the spleen give an almost classical syndrome of this condition.

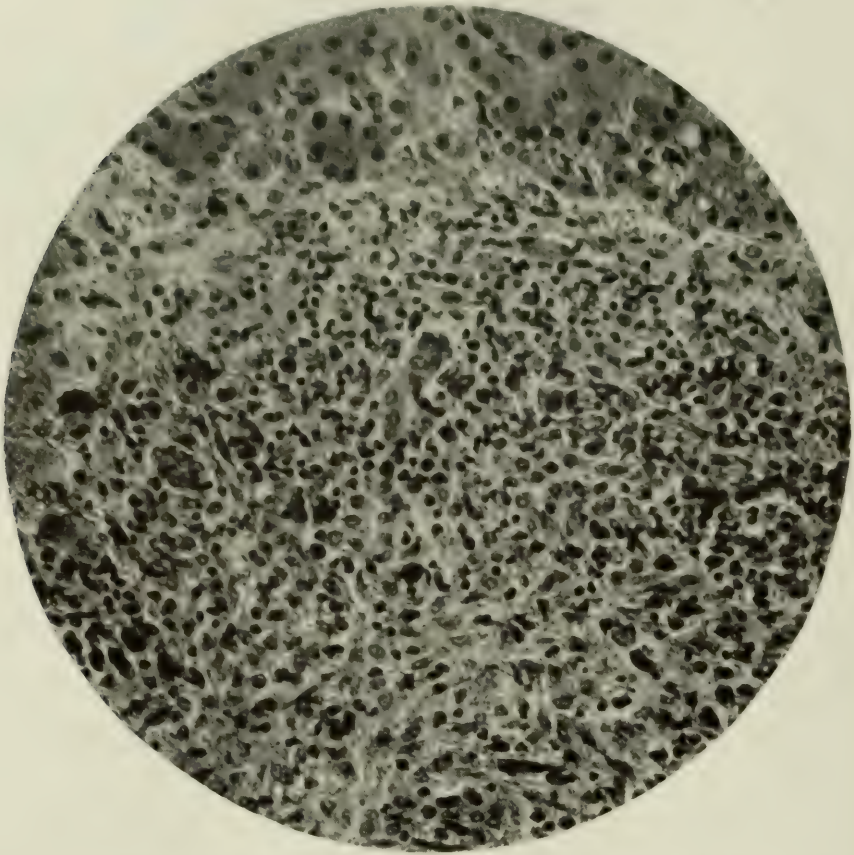


FIG. 3. Microphotograph showing focal area in liver, showing relation to liver parenchyma

The autopsy findings demonstrate beyond doubt the dominance of the splenic lesion. The thoracic lymph nodes were those usually designated as anthracotic nodes, densely pigmented and of small dimensions. The abdominal nodes were the largest seen and even these were only the size of a pea, certainly not the gross picture of abdominal lymph nodes in typical Hodgkin's dis-

case. The spleen was so large that it simulated a ventral hernia and was so thickly studded with lesions as to leave scarcely any splenic tissue visible. Therefore the assumption seems justified, from the gross anatomy, at least, that the lesion in this case was predominant in the spleen, and possibly started from that point.

On the result of the histological examination many theories may be formulated. The presence of the calcific tuberculous

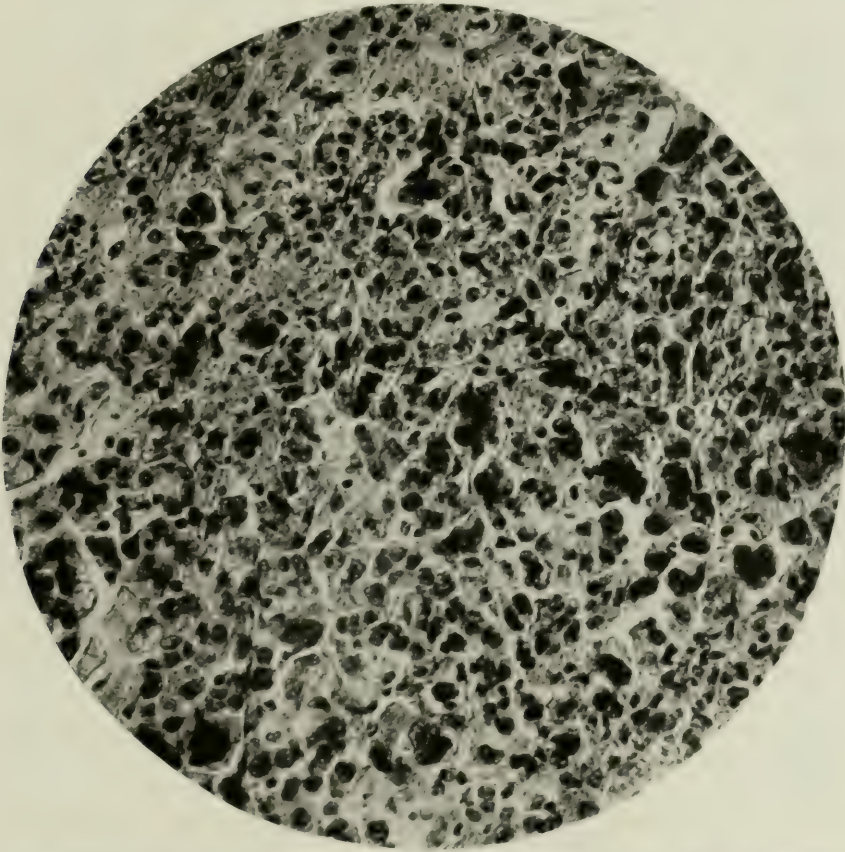


FIG. 4. Photograph of nodule in liver with large giant cells predominating.

lymph node in the mesentery suggests the possibility that this unusual condition may be an atypical type of tuberculous infection, producing a peculiar reaction in a resistant individual. With this possibility in mind and the knowledge of the close relation existing in many proven cases between tuberculosis and Hodgkin's disease, animal inoculations with emulsions of the splenic lesions were made. Guinea pigs, rabbits, and young chickens were used for this purpose, unfortunately with negative

results even after long observation (nine months). Sections were examined for tubercle bacilli and Mùch's granules, but also with negative results. This seemed rather convincing evidence of the non-tuberculous nature of this case. Furthermore the microscopic structure bears only the faintest resemblance to any type of tuberculous lesion.

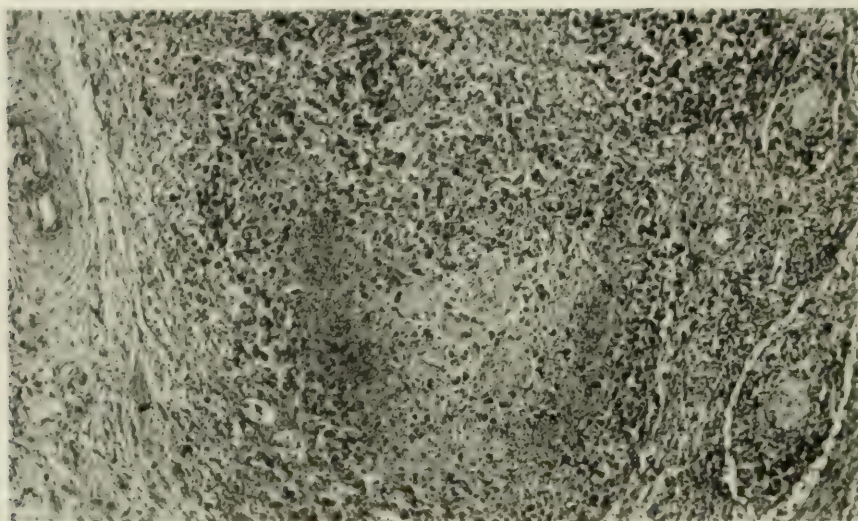


FIG. 5. Retroperitoneal lymph node. The capsule is intact and the sinuses are filled with masses of polyhedral cells

The smaller nodules in the liver and retroperitoneal nodes composed of large polyhedral cells with hyperchromatic nuclei and active mitosis leads one to suspect a true neoplasm possibly arising in the spleen with extension to neighboring lymph nodes and the liver. Against this theory we have the remittent type of pyrexia. It is extremely unusual to encounter long-continued fever associated with malignant neoplasms except in the very last stages, when it is frequently due to an intercurrent infection. This does not seem probable in this case.

Furthermore the vast majority of neoplasms, both benign and malignant, maintain histologically an overgrowth of a single type of cell to the exclusion of all others. In the lesions under discussion we have not only what appear to be large endothelial cells, but also giant cells, lymphocytes and plasma cells, giving the structure of a granuloma. Still the active mitosis and in-

tense hyperchromatism of the nuclei suggest a greater proliferative capacity on the part of these cells than is usually encountered in an inflammatory process and might warrant the interpretation of sarcoma. It is a well-known fact that many cases start as a typical Hodgkin's granuloma with characteristic histology in the early nodes examined. As the disease progresses the histology changes and comes to more nearly resemble a neoplasm until in the last analysis one finds he is dealing with what is commonly interpreted as Hodgkin's sarcoma. It is reasonable to suppose in these cases that one type of cell becomes dominant with greater loss of growth restraint until a chronic inflammatory process becomes a neoplastic one.

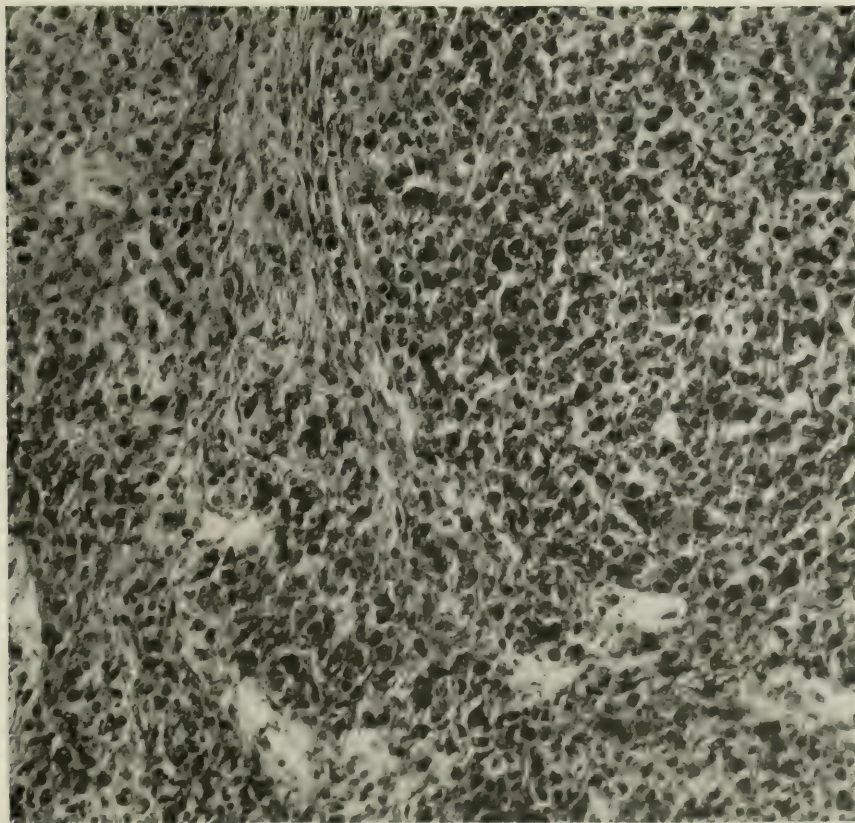


FIG. 6. Retroperitoneal lymph node. Bands of connective tissue are separating masses of hyperchromatic cells in the lymph channels.

In the case under discussion we appear to have an intermediate stage. The predominant morphological characteristics in

the spleen are those of a more or less typical Hodgkin's granuloma, while the lesions in the lymph nodes appear to possess greater neoplastic characters.

It is greatly to be regretted that the bone marrow was not examined in this case, in view of the recent observations of Symmers relating to bone marrow changes in Hodgkin's disease. I cannot quite agree with him that the large mononuclear cells encountered so frequently in these lesions are derivatives of the myelocytes. Undoubtedly one finds cells in the vascular and lymph channels, but that the polyhedral cells in the focal lesions are myelocytic in origin seems difficult to prove. Summing up the clinical and pathological findings and reviewing the literature I feel justified in considering this case as histologically a granuloma malignum primary in the spleen with extension to adjacent nodes and the liver with remittent type of pyrexia, and that it may be designated as a pyrexial type of Hodgkin's disease primary in the spleen.

Discussion:

DR. EWING: Were there any cultures of the tissue, or bacteriological studies, made?

DR. KLEMPERER: I would like to ask about the blood findings. The leucopenia was thought to be characteristic by Frank in severe cases of Hodgkin's disease. I would also like to ask how you would explain the jaundice in this case.

DR. PLAUT: I would like to know if there was no scar formation at all.

DR. L'ESPERANCE: Concerning the leucopenia, it is characteristic of this type of disease, and it has been noted in most of the cases in the literature. In my case the patient had a blood count when he first came in of 2,000,000 red cells, and the leucocytes were less than 5,000. This steadily dropped, until at the final attack he had a leucocyte count of 2,000, and the red cells also dropped to 1,000,000 at that time. His hemoglobin was correspondingly low, about 35 per cent. in the last attack. He seemed to be so well between the paroxysms that it was a most astonishing condition. There was apparently nothing but the enlarged spleen and a little epigastric discomfort in the interim.

In regard to Dr. Ewing's question as to cultures and animal inoculations, we suspected, on account of the calcified tuberculous node found in the mesentery, the possibility of this being a tuberculous lesion of an atypical form in a resistant individual, and we made fresh emulsions of the splenic lesion, and injected them into various types of animals. We used guinea pigs, rabbits, and chickens, the latter because I had an idea that it might be an avian type of tuberculosis. Unfortunately these animals remained absolutely negative

for nine months' observation. Sections were also made of the tissues and examined with carbol fuchsin and cresyl violet stain for tubercle bacilli, as well as Mùch's granules. We found neither. We are quite convinced therefore that this case is not one of tuberculosis.

There was no scar formation in the spleen. Besides the typical lesion the main thing in that organ was the intense congestion. The liver showed practically no scar tissue. The only attempt at scar tissue was that found in the retroperitoneal lymph nodes, which had a peculiar hyalinized capsule with trabeculae extending into the nodes. That was the only suggestion of hyalinization that we found.

DR. PLAUT: It seems to me that the lymph nodes which were so small may have been the first organ to contain the lesion, since they are the only ones to show a point of regression. We are generally accustomed to consider the point where we find scar tissue formation as the end point. Certainly it would be very astonishing and remain a mystery why a lesion in the spleen which is not the first one should be large, and the lesion in the lymph nodes remain small.

DR. L'ESPERANCE: We are accustomed to consider that fibrosis occurs in the later lesions of Hodgkin's disease, but it seems scarcely conceivable that any amount of fibrosis would obliterate the massive nodes of Hodgkin's disease, so as to leave a mass the size of a pea. That is the main point against that idea. Then the atypical quality of the cell, the lack of a granulomatous character, rather suggested that it was not a primary lesion.

CONGENITAL ATRESIA OF THE VESICAL EXTREMITIES OF BOTH URETERS

J. R. MEYER, M.D.

(From the Department of Pathology, Columbia University, and the Sloane Hospital for Women, New York)

With the use of modern methods of urological diagnosis, abnormalities of the ureters have lately been reported with increased frequency. Most of these are cases of complete or incomplete unilateral occlusion, when congenital, usually remaining without symptoms for several months or even years.

The case reported in this paper differs from most of the cases previously reported, in showing a congenital and complete obstruction of both ureters.

The prenatal history reveals nothing significant.

The baby was delivered December 31, 1923, after a normal labor, and except for absence of urination showed no other important abnormal con-

dition until nine days after birth, when hands, feet and face became swollen. Catheterization of bladder yielded no urine. The baby weighed 2,800 gm. at birth and 2,500 on the third day, gaining rapidly 150 to 200 gm. a day on the 5th to 10th days, in spite of insufficient breast milk and four to five watery greenish stools a day. The gain in weight coincided with general anasarca. Edema temporarily decreased after diaphoretic treatment. The general condition, however, did not improve and the baby remained pale and restless, regurgitating food until time of death, sixteen days after delivery.

The autopsy was performed fourteen hours after death.

The body is that of a full term, fairly well nourished male infant, weighing 3,100 gm., and measuring 46 cm. in length. Externally it shows nothing important but marked edema of face and limbs.

The thoracic and abdominal organs appear normal, but on account of restrictions on the autopsy nothing can be removed for examination except the kidneys, ureters and bladder.

The left kidney appears slightly smaller than normal, measuring 3.5 x 2.5 x 1.3 cm. It is firm and pale. On the external surface there are irregularly scattered throughout the lobes forming the organ a few cysts filled with a clear fluid, the largest of which measures about 0.3 cm. in diameter. Its capsule is easily detached. The cut surface is pale and shows two distinct



FIG. 1. Bilateral atresia of lower extremities of ureters. Posterior view.
A normal kidney is also shown to indicate comparative size

layers; one of a yellowish color measuring about 0.4 cm. in thickness represents the cortex, while the medulla measuring about 1 cm. is almost entirely white. No glomeruli can be distinguished on cut surface but a few small cysts.

The right kidney is much smaller than normal, and measures 2.5 x 1.5 x 1 cm. The external surface is pale and granular in appearance, showing a few cysts measuring about 0.2 cm. in diameter. The capsule is easily detached and on cut surface the appearance is the same as the left kidney.



FIG. 2. Low power topographic view of section of right kidney, showing cysts and fibrosis

The ureters are separated from each other through the upper third, while the lower two thirds are fused externally and appear to form a single structure (Fig. 1). From the top to the bottom they measure about 7 cm. in length. At the upper part where they are separated the right measures about 0.8 cm. in diameter and the left one 1.2 cm. in diameter. The single structure that is formed by their fusion measures about 2 cm. in diameter. It is irregu-

lar in contour, showing several dilatations at the anterior aspect, near its right margin, measuring about 1 cm. in diameter. An incision along the posterior surface exposing the cavity shows that the ureters are only fused externally, but internally are separated by a longitudinal partition. On the internal surface of both ureters there are sacculations and infoldings of the wall giving the lumina a rather tortuous course. Both ureters end in blind rounded pouches which do not communicate with the bladder on either side.

The bladder measures 2.3 cm. in length by 1.3 cm. in width by 1 cm. in the antero-posterior diameter. Externally it is smooth and normal in appearance. The mucosa is corrugated, and at each side of the trigone shows two openings through which a probe about 0.1 cm. in diameter can be passed for about 2 or 3 mm. The vesical end of the urethra is open and appears normal.

Microscopically both right and left kidneys show a marked increase of connective tissue, especially in the medulla around the collecting tubules. The glomeruli and convoluted tubules, which are surrounded by a rather loose stroma, both show definite abnormalities. While many of the glomeruli are normal, some are enlarged, surrounded by an increased amount of fibrous tissue and contain in the capsular spaces masses of homogeneous pink staining material surrounded by swollen epithelial cells (Fig. 3). The convoluted

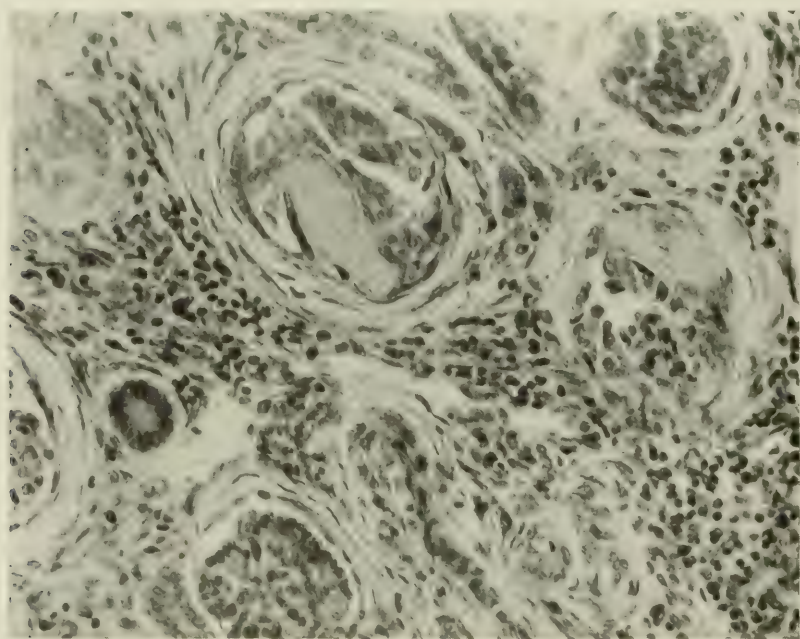


FIG. 3. High power photomicrograph of cortex of left kidney, showing damaged glomeruli, fibrosis, and presence of blood-forming cells.

tubules are lined by rather thick epithelium, the cells of which also appear swollen, showing in their protoplasm numerous small pink staining droplets. Among glomeruli and convoluted tubules there are small cyst cavities lined by flattened epithelium which attain larger dimensions near the capsule, where they are surrounded by a thick layer of connective tissue (Fig. 2).

Scattered throughout both kidneys there is a large amount of blood-forming tissue consisting mostly of myelocytes and small mononuclear cells, probably normoblasts. In numerous areas around groups of tubules in both cortex and medulla are many polymorphonuclear leucocytes, probably also a part of the blood-forming tissue. At one point just beneath the capsule in the left kidney is a small mass of cartilage.

Sections of the ureters at different levels show a layer of dense connective tissue lined by epithelium which is made up of two rows of small, almost round cells. In the connective tissue there are small groups of mononuclear cells suggesting blood-formation.

The bladder contains an increased amount of connective tissue surrounding its muscle bundles. There is a lining epithelium several cells in depth, made up of columnar cells resting on a thick layer of connective tissue in which there are many blood-forming cells.

As the description of the case indicates, there is apparently a primary lesion consisting in a lack of communication between ureters and bladder, and other changes probably secondary, consisting in dilatation of ureters, degeneration of the secretory epithelium and fibrosis of kidneys. Present also, but not possessing the same importance as the other lesions, is an abnormal developmental condition of the kidneys shown in the presence of a small area of cartilage, and in the cystic dilatation of the urinary tubules, and the presence of a large amount of blood-forming tissue.

We believe that the chief lesions in this case are probably the result of a simple defect of development of the ureters occurring in an early stage of embryonic life.

As is generally known, the first vestiges of the urinary apparatus are the nephrotomes, that is, paired masses of cells developed in the mesoderm and at each side of the so-called mesodermal segments. These masses form the pronephric tubules which after growing backwards form another pair of structures known as the Wolffian or primary excretory ducts. The former (pronephric tubules) soon undergo involution and disappear while the latter (Wolffian ducts) still persist, even continuing their development by a process of terminal growth towards the caudal extremity, until they reach and perforate the cloacal horns. Before reaching the cloaca these ducts form an angle from which the ureters later

develop as evaginations, one at each side, growing at first dorsally and afterwards towards the cephalic extremity.

According to Felix (quoted from Prentiss) in an embryo 2.5 mm. in length the development of the primary excretory (Wolffian) duct is almost complete and in 4.25 mm. embryos these ducts have already reached the cloaca fusing with it. It is clear that this fusion may fail and consequently no communication will be possible between ureters and bladder. This is what we believe to have happened in this case, and even if there is no direct proof to confirm such an explanation, it seems the best and most logical one.

The cause back of this failure of union is not evident. Several authors, referring to similar conditions, believe in the possibility of congenital syphilis which, as has been proved, has a conspicuous effect on the life of the embryo, leading to a retardation of its development.

Inflammatory processes other than syphilis, or intrauterine trauma during a very early stage of life, may also be considered as a possible cause. Nevertheless, these views must not be accepted without reservation owing to the difficulty of demonstration.

So far as the bibliography is concerned, not many cases of congenital strictures of the ureters have been previously reported. Most of them are considered in Bottomley's paper, which consists of 56 cases he collected previous to 1910. From that time until 1917 Eisendrath reports 4 cases of his own and mentions 7 others on record. Since the publication of Eisendrath's last paper on the subject, 10 new cases may be added, thus making a total of 77. These cases, however, differ from our own as they deal with unilateral or incomplete occlusion, most of them remaining without symptoms for months or years.

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CHEMICAL FACTORS IN BONE PATHOLOGY *

WALTER H. EDDY

Since the publication of the British Medical Research Committee's Report in 1919 increasing attention has been given to the problem of bone formation with a special consideration of the phenomenon known as rickets. It is not my purpose this evening to review this work on rickets; that has been done frequently in the past few years by the active workers in the field. I do

* Presented October 9, 1924.

wish, however, to discuss this evening certain correlated phases of the problem, covering in particular some experimental data in the field of fracture healing conducted at the New York Hospital with the assistance of Dr. C. R. Murray, and from which I wish to draw certain conclusions as to what must be done before we can hope to formulate definite procedures in controlling bone formation.

Sherman and Pappenheimer were among the earliest (March, 1921) to show that the deposition of calcium in bone could be effected by merely changing the phosphorus content of a special diet. Their diets were as follows:

	No. 84 Per Cent.	No. 85 Per Cent.
Patent flour.....	95.0	95.0
Ca lactate.....	2.9	2.5
NaCl	2.0	2.0
Fe citrate.....	0.1	0.1
K ₂ HPO ₄	0.0	0.4
Total phosphorus.....	86 mgs. and 157 mgs. per 100 gms.	

No. 84 produced rickets, No. 85 prevented rickets.

It will be noted that a change of 70 mg. per 100 gm. of ration was sufficient to produce, or prevent, the deposition of calcium. The Sherman-Pappenheimer diets were also deficient in vitamins A, B and C and in protein and potassium. It therefore did not absolutely follow that the etiological factor was phosphorus. In January of the same year there was published by McCollum, Shipley, Simmonds and Park a series of diets which produced abnormal skeletal conditions in the rat apparently identical with the picture of human rickets. All of these diets were deficient in vitamin A. One was defective in its phosphorus content though the significance of this was not recognized at the time. The others were defective in calcium. The proteins were all of good quality. From these results the writers drew the following conclusion: "At present it is only possible to say that the etiological factor is to be found in an improper dietetic regimen. The large number of dietary formulæ, the administration of which results in rickets and kindred affections, gives abundant

evidence of the complex nature of the causes operating in the production of the disease." In publications that followed by Pappenheimer, McCann, Hess, Zucker, and others, vitamins A, B, C and potassium were eliminated as factors. The Hopkins school followed with kindred papers and established the relation of the disease to the calcium and phosphorus in the diet, both confirming the disease produced by diet 84 as a low phosphorus rickets and also showing that rickets could result from either low calcium or low phosphorus. Since these papers appeared, much progress has been made in the study of calcium and phosphorus as dietary constituents and their relation to bone formation. Some of these data I should like to discuss later. For the present I am calling attention to these observations as bases for the interest in phosphorus as a part of the problem of bone formation.

The next viewpoint that I wish to discuss might, therefore, be considered as a consequence of the proved relationship of the two mineral elements mentioned to bone formation. In brief, if calcium and phosphorus in a diet are related to effective and defective bone formation, it would be natural to expect that the blood which supplies the bone-forming elements to the individuals would reflect this relationship. That such a relationship exists has been abundantly demonstrated by Hess and his co-workers, and by Howland and Kramer of Johns Hopkins. In brief, in cases of rickets there is a marked diminution in the phosphate content of the blood and under curative treatment there is a rise in this phosphate content toward normal. Furthermore, there seems to be a fairly constant normal content of this element in the blood, the amount being fairly high in infancy and up to about twenty years of age. This is the period of active skeletal formation. After this period it drops to a lower figure. From figures presented by Howland and Kramer, Tisdall assumes an average of about 5.4 mg. of inorganic phosphorus per 100 c.c. of serum up to the age of twenty years, and for adults of more than twenty years of age an average of about 3.8. Tisdall's average for normal persons above the age of twenty is a little higher than has been found by other workers. Hess has also

shown that for infants some modification of the 5.4 average is necessary. In the *Journal of Biological Chemistry* in the year 1923, Tolstoi gives figures based on 100 adult cases showing a range of from 2.5 to 3.3 mg. per 100 c.c.

These results obtained in the study of normal cases and rachitic cases above mentioned stimulated interest in the phosphorus content of the blood as a possible index of success or failure in cases of bone pathology other than rickets. In 1922 there appeared a paper by Tisdall and Harris in the *Journal of the American Medical Association* in which these authors made an attempt to evaluate the inorganic phosphate of the blood as a specific index of fracture healing. In this article, while admitting, first, that the exact means by which calcium salts are deposited in areas of bone growth or bone repair is to a large extent unknown, they adopted as their thesis that while part of the process must take place at the site of growth or fracture, there is good reason to believe that changes in the inorganic metabolism of the body may accompany and perhaps determine the deposition of bone salts in fracture healing as well as in rickets. If such be the case there should be a direct correlation between the inorganic phosphate content of the serum of patients recovering from fractures and progress in fracture healing. We might also expect excessive bone formation to show excessive blood phosphorus. As is shown in the charts submitted¹ by these authors, they found in general, first, that following the fracture there is an immediate rise in the inorganic phosphate of the individual's blood; second, that there is a progression about this rise which keeps pace with the progress of the healing, rising steadily up to about the 21st day and gradually declining to normal after that period. During this period the calcium content is only slightly varied, remaining at about a normal of 10 mg. per 100 c.c. The investigators were, however, careful to call attention to the fact that the phosphate content of the blood is not the sole factor involved in satisfactory fracture healing. From the study of dogs in which experimental fractures of the humerus

¹ *Jour. Am. Med. Assn.*, 1922, liii, 884.

were produced, they demonstrated not only a rise in blood phosphate, but, in spite of this increase, found that union was delayed in cases where imperfect apposition occurred. In brief, they consider that there is both a metabolic change and a local factor involved in fracture healing. They also report one human case where there is a rise in phosphate, but with no union, and frankly raise the question as to whether the blood may be used to predict non-union without attempting to answer it conclusively.

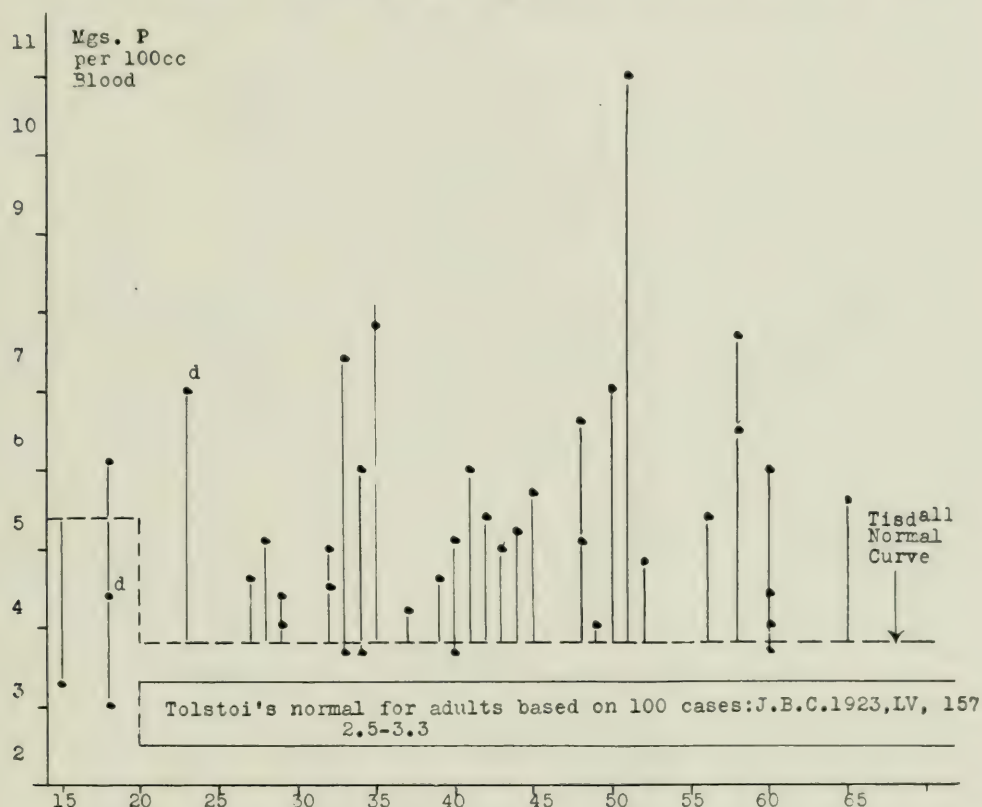


CHART I. Inorganic phosphorus in serum in 40 fracture cases of varying age and character of fracture

These observations of Tisdall and Harris naturally aroused interest among the surgeons at the time of their publication. At the New York Hospital, with the assistance of Dr. Murray, I began the study of selected fracture cases with a view of confirmation, or better, interpretation, of the Tisdall-Harris results. In making our determinations we had first the problem of selecting the best method for analysis. We had available at that time

the Briggs modification of the Bell-Doisy method and the method of Tisdall. Since we were to cover the same field as reported by Tisdall and Harris, we preferred to use the Tisdall method. A series of checked tests, using his method and that of Briggs, gave us results sufficiently close to justify our faith in the accuracy of the Tisdall method. We were also aware that blood serum, on standing, changed in phosphate content, and so far as possible all our phosphate determinations were made on blood serum as soon after collection as possible, and almost uniformly within 24 hours of the collecting time. Fracture cases were selected by Dr. Murray with a view to illustrating types, and to making our observations of as general application as possible. Some 40 odd cases in all have been so studied.

Let us now consider the gross results as shown on Chart 1. These results undoubtedly confirm the observations of Tisdall and Harris as to rise in blood phosphate during the fracture healing period. Assuming their normal blood content as correct, the phosphate determinations are, with very few exceptions, well above the normal, and their conclusions are still further substantiated by our cases if you take Tolstoi's normals. We can also state that in the cases where successive determinations were made at intervals during the progress of fracture healing, there was a rise and fall corresponding to progress of the case, as found by Tisdall and Harris. When, however, we review these cases from another viewpoint, *viz.*, does the increased phosphate always parallel the amount of bone formation—that is, do we find the phosphate higher in individuals with excessive bone formation than in those with less bone formation?—our correlation is much less apparent. (See Table I.) Such a study makes us decidedly skeptical as to whether the phosphate rise is the limiting factor in calcium deposition. Certain observations also made by us raised at the time the question as to whether this phenomenon could be associated not only with bone formation but with tissue formation in general. We therefore next extended our blood analytical studies to a series of cases of operative surgery in which the tissue formation was not bone. The results of these

TABLE I
Features of the Fracture Cases Reported²

Case	Age	Bone	Char. Fr.	Amt. Callus	P	Excess Bone
1....	35	Tibia	Simple	L	7.8	O
4....	18	Both leg bones	Simple	S	3.02	O
5....	15	Humerus	Simple	L	3.3	O
6....	33	Skull and rib	Simple	S	4.2 7.4	O
7....	32	Both legs	Comp.	L	5.0	O
8....	56	Radius	Comp.	L	5.35	O
9....	52	Femur	Comp.	LL	4.76	L
10....	40	Ulna	Simple	L	4.6 5.1	O
11....	60	Radius	Comp.	L	4.00	O
12....	44	Humerus	Old non-union		5.2	O
13....	48	Femur	Simple	L	5.08	O
14....	28	Cervic. Rib	Comp.	L	3.32-5.12	O
15....	37	Os calcis	Simple	L	3.6-4.2	O
16....	18	Fibula	Simple	S	6.1	O
17....	35	Skull	Simple	S	5.4-7.8	O
18....	60	Neck femur	Simple	S	3.67	O
19....	58	Colles	Simple	L	7.68	O
21....	29	Scaphoid	Old non-union	L	4.4-4.34	L
22....	49	Mult. contusion	None	O	3.9-4.0	O
23....	30	Metacarp	Simple	L	4.1-7.1	O
24....	50	Colles	Simple—delayed	S	7.0	O
25....	58	Potts	Simple	L	6.52	O
26....	40	Os calcis	Simple	S	3.7	O
27....	34	Tibia	Simple	S	3.7	O
28....	65	Both legs	Comp.	LL	4.1-5.6	L
29....	33	Colles	Simple	S	3.7	O
30....	51	Humerus	Comp.	LL	3.9-11.04	LL
31....	42	Both bones	Comp.—delayed	L	3.7-5.4	O
32....	29	Femur	Simple	S	3.96	O
33....	32	Metacarp	Simple	L	3.3-4.5	O
34....	60	Colles	Simple	L	2.3-6.0	O
35....	60	Neck femur	Simple	L	4.6	O
36....	52	Path fr. legs	Tumor—no bone	O	3.31	O
37....	39	Colles	Simple	L	4.6	O
38....	48	Fib.	Simple	S	6.5-6.6	O
39....	27	Fibula	Simple	S	4.6	O
40....	18	Humerus	Comp.—delayed	S	4.46	O
41....	16	Femur	Large	LL	4.2-6.1	O
42....	34	Both arms	Comp.—delayed		3.7-6.0	O
43....	43	Scaphoid	Simple	L	2.6-4.9	O
44....	45	Humerus	Comp.	LL	5.7	LL

studies are shown graphically in Chart 2. They indicate that there is something about the regeneration of tissue other than bone that calls out the phosphate reserves of the body. It occurred to us, therefore, that if we could secure cases in which there was a large area of tissue regeneration, such as in the case

² In Table I the letters used signify the following: L, large; LL, very large; S, small; O, none.

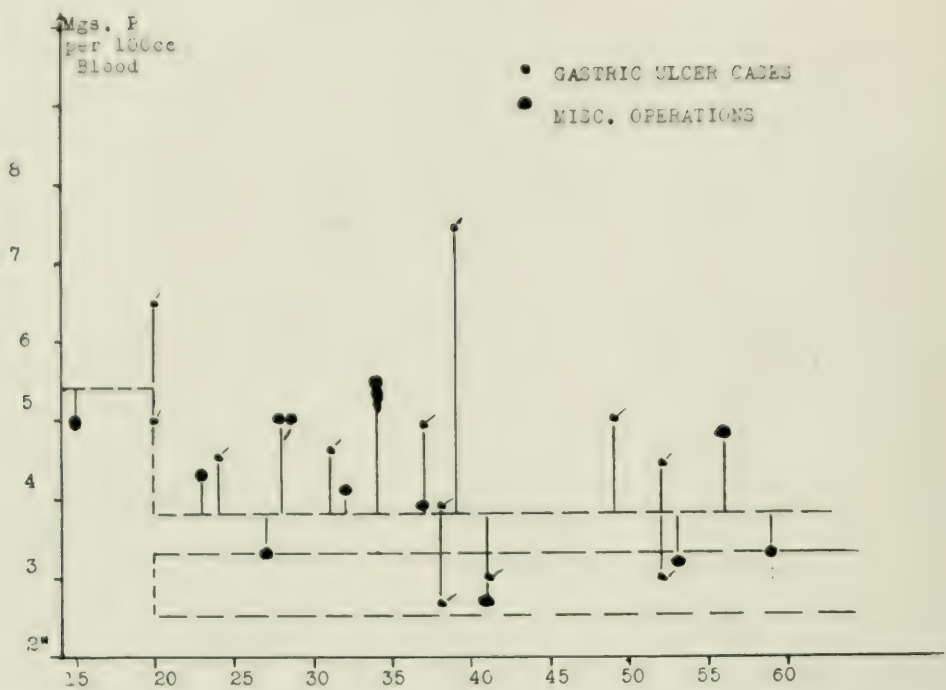


CHART 2. Inorganic phosphorus in operative cases

of burns, we could get additional light on the relation of phosphate to tissue formation. Two cases involving recovery from burns of large area provided interesting data for individuals of the same age differing only in rate of healing. The results are given below :

TABLE II

	P.	Ca.	Age
1. Rapid healing burn.....	5.75	14.4	30
2. Slow healing burn.....	3.44	9.6	30
4. Tuberculous, bed cases.....	3.25		
	4.87		
	4.30		
	5.09		
	4.15		
	4.31		
5. Ambulatory cases.....	3.70		
	3.53		
	3.59		
	3.37		

These results seemed to confirm the viewpoint developed from the study of the operative cases. It was then suggested that in tu-

bercular cases we might find the same relationship between phosphate and the progress of recovery, our assumption being that in the improving or less severe cases we would get an increase in phosphate parallel with ability to deposit calcium, while in the more acute cases this situation might be reversed. We have only limited data on this phase of the investigation as in the case of the burns, but these data presented unexpected results. (See Table II.) In other words, our bed cases showed higher phosphate than the ambulatory cases. On the assumption that the blood phosphate is an index of calcium deposition the results certainly are negative. On the other hand the bed cases were probably breaking down and regenerating larger amounts of tissue. On the hypothesis that tissue formation is a cause of the phosphate rise the results check the burn cases and the operative cases.

We are well aware that we have to date a distinctly incomplete interpretation of the Tisdall-Harris phenomena. In fact we have already certain supplementary experiments planned and have delayed publication of our results in the literature until more data could be accumulated.

From the results here, however, we believe we are justified in the conclusion that while the rise of phosphate usually accompanies fracture healing, it is most unreliable as an index, or as a means of prediction of mal-union or non-union or of extent of bone formation. The results also have made it clear that attractive as the hypothesis is that phosphate determinations be made a clinical test for progress in fracture healing, such a clinical test is at present entirely unreliable and a satisfactory test must await the attainment of a much clearer conception of mineral metabolism and the factors involved therein. It is well established that in rickets the failure to deposit calcium in bone is accompanied by a lowering of the inorganic phosphate of the blood and that as soon as healing begins the blood phosphate also rises. It is quite another thing to argue that calcium deposition is the sole factor that can produce a rise in blood phosphate, or even that in cases where calcium is being deposited, the blood phosphate is an index of the rate.

In presenting the experimental data above recorded before this group we have been activated, not by a desire to contradict or question established pieces of research in mineral metabolism, but on the contrary we feel that these results stress the importance of such studies and that pathologist, surgeon, and nutrition specialist must cooperate even more completely than in the past to clear up the many complexities of the problem. Tremendous advance has already been made in the studies which will provide tools for prophylaxis or curative measures to the practitioner who is concerned with either dentition or bone pathology. In concluding this presentation I would like to cite a few of the outstanding contributions of the years that have succeeded 1921 to illustrate both what has been done and what needs to be done.

Controversy over Mellanby's findings which appeared in the British Medical Committee report has long since established the certainty of an antirachitic vitamin other than fat soluble A. Dr. Mellanby has recently stressed the importance of the vitamin factor as in his judgment far more significant than the calcium and phosphorus of the diet.

In work published by Betke, Steenbock and others in 1923, one may also find apparent support of the idea that the antirachitic vitamin factor, or its equivalent, the radiant energy of the ultraviolet light, is the important factor in calcium deposition, and that with these factors provided for, we need not pay so close attention to the calcium and phosphorus of the diet. I think in this connection that it is worth while to call attention here to a careful piece of work produced from Dr. Sherman's laboratory by Dr. F. L. MacLeod. In these studies a diet was provided which is known to be complete in all of the factors of an ordinary normal diet. Careful studies were also made of the calcium content of normal animals and of animals fed on this diet. It was then possible to show that when to the experimental diet one adds either one per cent. cod liver oil, or one per cent. calcium lactate, the calcium addition is more effective than the cod liver oil in producing calcium retention.

In his excellent review of the rickets problem in the *Physio-*

logical Reviews, 1923, iii, 106, Park has made a statement in regard to the relative importance of the factors in the diet which may well be quoted here:

"As the result of clinical observation and investigation it has become clear that two factors exist. The one in radiant energy, the other in an unknown form in certain foods, either of which is capable of preventing rickets from developing, or from continuing if already established—one at least of their functions appears to be the protection of the organism from the dangers attendant upon the absorption and entrance into the blood of substances which might disturb its salt balance. . . . Experiments have proved that in the rat a food, quite apart from vitamin, can precipitate the development of rickets or stop its development. . . . The whole subject of the etiology of rickets is extraordinarily complex, and the clear presentation of the facts, not to mention the correct interpretation, is most difficult. At the risk of falling into pitfalls, however, it seems wise to attempt to draw a parallelism between rickets and diabetes which will make clearer the views of the present writer. Diabetes is a deficiency disease in the sense that the internal secretion essential for the maintenance of normal metabolism is deficient. Rickets is a deficiency disease in the sense that radiant energy and the factor X are deficient. Diabetes is a disturbance in the carbohydrate metabolism. Rickets, as we know, is a disturbance in the metabolism involving, in particular, calcium and phosphorus. It is possible to influence diabetes by means of the diet in two ways: directly, by feeding diets rich in carbohydrate substances which the organism finds it most difficult to metabolize; and indirectly, by diets which are unsuitable in a general sense in that they do not meet the general requirements of the organism. In like manner it is possible to influence rickets by means of the diet in two ways: directly, by feeding diets having specific salt defects, or defects of an unknown nature which load down the disabled mechanism governing the salt regulation of the body; and indirectly, by diets which are unsuitable for the general requirements of the organism. In both diseases the diet can increase or diminish the metabolic disturbance according as it strains or spares the metabolism at its weak point; in both diseases the diet can increase or diminish the metabolic disturbance according as it fails or succeeds in meeting the general requirements of metabolism. In diabetes the diet is not the cause of the disease; the cause lies in an insufficiency of the internal secretion of the pancreas; so also in rickets, the diet (considered apart from X) is not the cause of the disease. The cause lies in the deficiency in the regulatory influence of radiant energy or the unknown factor—antirachitic vitamin in the food."

The above parallel is not only a fair evaluation of the importance of the various factors in rickets, but it also should emphasize that any data which will bear on the regulation of

mineral metabolism will prove as significant for practice in curative measures as will intensive study of radiant energy and of the antirachitic vitamin. In that connection I would like to call attention to the work of Scholl on the regulation of acid and base metabolism and the factors which influence the retention of base. Also the work of Zucker, and others, which has shown that the reaction of the intestine may have a profound influence on the absorption of the mineral elements from the food into the blood, whence they must arrive if they are ever going to reach the site of calcium deposition. Such studies have as much significance in the general problem as the more striking results recently published by Hess and by Steenbock, which have shown conclusively that foods devoid of the antirachitic vitamin may be made to produce their effects by irradiation with ultraviolet light. To solve the specific problem which I have presented tonight, and many others related thereto, we need a vast amount of information in regard to the locus of action of all these factors of calcium deposition and their method of functioning. Such information is at present non-existent. Its development can come only by a further combination of the forces of research which have made so great strides since 1921. I am presenting these data tonight to solicit your aid in contributing to the final solution.

Discussion:

DR. CLAY RAY MURRAY: This subject has a very definite surgical application, and one in which all surgeons doing fracture work are interested. One of the biggest problems in such work is the question of delayed unions, and non-unions, particularly the question of delayed unions, since by the use of x-rays it is almost impossible to keep track of the progress of early union in fractures, because of the fact that early callus cannot be shown through plaster splints by the ordinary x-ray. It is possible to demonstrate the development of callus without splints in place, but once the splints are applied, the use of x-ray, which can be cut down from the standpoint of penetration, no longer helps. The report in the *Journal of the American Medical Association* stressed the point that one might be able to prognosticate union from calcium determinations of the blood. So far as union is concerned, the whole proposition can be discarded. After ten years' study on a very active surgical service, I have come to the conclusion that the question of real non-union, that is, without any formation of bone, is purely a mechanical problem, and has nothing

to do with anything but the local condition. In the question of delayed unions, there exists a parallel to the rachitic condition. It is a question of calcium deposition. Where the problem is meant to apply to a situation where osteoid tissue forms the framework of the bone which is laid down but a deficiency lies in the calcium deposition and the formation of solid bone tissue, the possibilities of this problem are very great, as it is then brought in a parallel with the rachitic problem with which the normal formation of bone does not compare at all.

The cases are chosen from the standpoint of showing varying degrees of bone formation and of calcification, and also showing cases with a great deal of tissue formation without any actual calcium deposition. There is one case which is not shown here, because it is not a fracture, but I would like to mention it first because of the remarkable findings in it. The patient was a man of middle age who had been kicked in the thigh by a horse, and had developed a tremendous myositis ossificans. His phosphorus determination, taken at the height of bone formation, was 2.73 mg. He was not only the case which showed the most bone formation, but also showed the most extensive calcification of tissue, and his phosphorus determination comes close to being the lowest in the series. The cases, as you see from the chart, vary tremendously in their findings. The first case is one of a spiral fracture of the tibia with no displacement and no bone formation outside the line of fracture and this patient had the relatively tremendously high finding of 7.8. In case 9, one of fractured femur, with a double spiral fracture showing a large amount of bone formation, the phosphorus is a low normal. Case 12 is a case of old non-union, but which had a second fracture during the still delayed union of the first, the second fracture having an excessive amount of soft callus, but with little or no calcium deposit in it. The *x*-ray at no time demonstrated any appreciable amount of calcification, and yet the findings are much more above normal than many cases showing true bone with normal ossification. Number 23 is a simple metacarpal fracture showing high findings. There is a line of fracture with no bone to be seen in the *x*-ray picture taken without splints with a proper ray, so that the penetration was slight and the ray was soft; any calcification would have been brought out if it had existed. Number 19 was a Colles' fracture, and is probably the only case of Colles' fracture I have seen in the last ten years in New York which showed a real non-union. At the end of twelve weeks that case had no union at all. His calcium findings were 7.68 mg. There was absolutely no bone formation, and only fibrous tissue between the two fragments. If you follow the series of cases, you will find the same lack of correlation, so from the surgical standpoint it seems to have practically no significance as to union or non-union, or as to delayed or normal unions.

The point which Dr. Eddy brought out in relation to tuberculous cases verifies what we have found here in the lack of correlation. In those ambulatory patients whose lesions heal and become fibrous and calcified, there is the low figure. Those patients who are active and run a temperature, all showing a tremendous amount of tissue formation in the form of tubercles, and no effort at fibrosis or calcification, show the high phosphorus findings. That is, those showing ordinary tissue formation run high.

We hope to extend the scope of this work from the surgical standpoint to check up on the factors which give this rise in calcium, and see if we can correlate more closely tissue formation in general as opposed to the process of pure bone-healing. It seems preposterous for a fracture of the metacarpal with no displacement and no disturbance, and no clinical symptoms, the surgical pathology of the lesion being a very moderate amount of swelling, to give rise to the tremendous physiological response on the part of the body which would raise the blood phosphorus to the point shown here, when, on the other hand, a number of instances of spiral fracture of the femur with great displacement and a large pathological lesion showed only a relatively slight response. The table as a whole from the surgical standpoint fails to bear out the hopes that Tisdall's paper held forth. Yet the problem holds a tremendous interest for surgeons interested in the question of fracture work, and I hope that it will be followed out to see if there is anything in the work which can be made of use.

DR. HESS: This question of ossification in bone, as you can all appreciate, is a most difficult one to discuss. The whole subject is in a state of flux, and the aspects are so many it is very hard to focus the discussion on any one point. There is the question of the source of the vitamins, and of radiant energy, each one of which is sufficient for a discussion of one evening. There has been, however, a very significant change in the general point of view, more particularly in regard to rickets, in the last three or four years, since rickets has lent itself to experimental study. In the first place, attention has been focussed on the phosphates, rather than on calcium. Until recently almost all the workers experimented and studied the calcium balance, forgetting that the bone is composed almost entirely of salts of calcium and of phosphate, and that the phosphate must necessarily play an important rôle in its formation. Schabad was probably the only one who kept writing on the importance of phosphorus in the development of rickets. Secondly, the change has been a turn to biological experimentation. Previous to that time, the work had been on the metabolism of infants, and to a less extent, of animals, that is to say, a study of the intake and output of various salts. Now we read little of that, and the work has turned either to biological experiments, as Mellanby's work on dogs, or to the determination of the inorganic phosphorus in the blood. Probably we have gone too far in that direction. It is very probable that a point will be reached in experimental work where it will be necessary for us to do metabolism work in infants in order to check it. I think it is a very fair criticism against the work on experimental rickets-producing diets that they are either poor in calcium or in phosphorus, and that this cannot be the way in which rickets is brought about in infants, because we know that they most certainly get enough phosphorus and calcium. The very fact that a great deal more rickets develops in bottle-fed babies than in breast-fed babies, and that cow's milk has three or four times as much calcium and phosphorus as woman's milk shows that they can not play an essential rôle in the development of human rickets. Nevertheless, all the rickets produced in the laboratory depend on these factors.

Then in regard to the study of the inorganic phosphorus of the blood, this after all is one of the smallest moieties of the blood. The organic phosphorus is in far greater amount, and we know nothing about the function or the amount of this factor, which is again composed of various components in the blood of normal and rachitic individuals.

There are in general three things to be considered in the development of rickets: the salts, the vitamins, and the question of radiant energy. Personally, although I may be somewhat biased, I think what promises most is an understanding of the action of radiant energy, of the ultraviolet ray; if we knew in some measure how this acts, we might comprehend more about the entire subject. Dr. Eddy spoke of the work of Steenbock in radiating foods. Some time ago I recorded similar results. If we took cottonseed oil, or linseed oil, vegetable oils that have no antirachitic value, and radiated them for one hour with a mercury vapor lamp at a distance of one foot, and then fed this oil to rats, we found that it had changed from an inert oil to one that has definite antirachitic value. One tenth of a c.c. of this protected rats on a standard rickets-producing diet. It will maintain this power for at least twenty days. Another experiment may be of interest to you. If you take wheat and grow it in the light, it becomes green; whereas if you grow it in the dark, it is etiolated and yellowish and has hardly any color. If you radiate this green wheat and feed it in ten gram doses to rats, it will protect them against rickets, but if you feed the yellow wheat, it will not. If you take a vegetable leaf, such as green lettuce, and feed it in ten gram doses in connection with a rickets-producing diet to rats, they will all get rickets. These green leaves treated with ultra-violet light will acquire an antirachitic potency.

That does not as yet get us very far with the question of ossification. There are experiments of a somewhat similar nature recorded recently from Yale. I think all of these studies may show us before long how radiant energy works. If we could find out how one of these factors—radiant energy, or the vitamins—works, it might give us some clue as to the mode of ossification.

DR. PAPPENHEIMER: I have been much interested in Dr. Eddy's study, and especially in his theory associating the rise in inorganic blood phosphate following fractures or operations with the new formation of tissue in the process of repair. It does not seem to me, however, that he has brought very definite evidence in support of this view. There may be one or two other possible explanations which could be proved experimentally, or by the study of clinical cases. Is it possible that blood shed into the tissue spaces may provide a source of inorganic phosphorus through the breaking-up of the acid-soluble organic fraction contained within the red corpuscles? It would be interesting to know also the effect of anesthesia upon the blood phosphate. If Dr. Eddy's suggestion that the rise in phosphate is correlated with the formation of new tissue in the body be true, one may reasonably expect such a rise in actively growing tumors where there is an abundant proliferation of new tissue. I should like to ask Dr. Rohdenburg who has, I believe, worked on the mineral metabolism of tumors, whether he has observed such a rise.

DR. ZUCKER: Anything which bears on the mechanisms which control the levels of various blood constituents is of extreme interest. We have no hypotheses which throw any light on their nature, except in the case of carbon dioxide, but we know that they must be very accurately working mechanisms. When the paper of Tisdall and Harris came out, a good many of us thought that here were some facts bearing on this subject as far as the phosphate is concerned. Tisdall's data would link up beautifully with the fact that in the infant where there is active bone formation the phosphate is also high. Now that Dr. Eddy has shown that Tisdall's work does not hold, it is probably better to drop the hypothesis that increased demand for phosphate on the part of the bone will raise the level of blood phosphate in the same manner. The opinion of Howland and Kramer that the curing of rickets was due to a rise in inorganic phosphate in the blood which then permitted a deposit of calcium phosphate in the bone has also fallen away because animals in which rickets has been produced can be given cod liver oil or radiant energy to a very considerable degree and produce a good deal of calcification before the inorganic phosphate and calcium will come anywhere near the solubility product which they postulate for calcium phosphate in the blood. Another point Dr. Eddy spoke of was the subject of the various factors in the production of rickets. There has been a long struggle between English and American workers on the relative significance of these various factors. In the beginning, due to Mellanby's work, the center of gravity of the whole thing in England was vitamine content of the diet, in particular, the content of the fat soluble vitamine A, attributing very little, if any, primary significance to the mineral composition of the diet. The deadlock on the question of fat soluble vitamine has recently been broken by Drummond's admission that the fat soluble vitamine is not the antirachitic factor. The work of Mellanby with regard to oats and whole wheat will have to be re-interpreted because by far the greater part of the phosphorus in such a diet is not present in the form of inorganic phosphate which can be absorbed, but mostly in the form of organic phosphorus compounds, which, as Dr. Eddy has shown some time ago, do not at all play the same rôle in rickets prevention as does phosphate in inorganic form.

DR. ROHDENBURG: I might offer to Drs. Murray and Eddy the suggestion that the parenteral introduction of any antigen will cause a profound disturbance of the salt metabolism of the individual. An incised wound means the death of a certain amount of tissue, which, though it may be infinitesimal, will cause a disturbance of the mineral constituents of the blood, for example, the injection of one tenth of a c.c. of blood produces in a rat a hyper-mineralization of almost 200 per cent. in the mineral content of the blood. Living and dead protein behave in a somewhat different manner. The calcium content of the blood of animals and of human beings bearing rapidly growing tumors shows not very much difference from the normal. If animals injected with protein are normal and have no locus of rapidly proliferating cells in the body, the injection will produce a disturbance of mineral metabolism. If, on the other hand, they have a focus of rapidly proliferating cells within the body

(pregnancy, tumor, transplanted or spontaneous), the mineral metabolism is not disturbed by such injections.

Another point may be of interest to Dr. Hess, and that is that within twelve hours after radiation of a tumor with x -rays, there is a mineral disturbance in the tumor itself, initially a hyper-mineralization, and subsequently a demineralization.

DR. EDDY: We fully realize that we have not produced much that is constructive, but we have at least thrown open the question as to the Tisdall and Harris view, and our idea in presenting the paper was for the exact purpose as developed in the discussion. I was particularly interested in the suggestion from Dr. Rohdenburg. We did have one case of cancer in our series, with a phosphate of 5.0.

CARCINOMA OF THE LUNG WITH METASTASES *

D. S. D. JESSUP, M.D.

This case of lung tumor has the following points of interest. The patient was under observation for six months before death with both clinical and x -ray examinations so that the progress of tumor growth could be studied. There was marked involvement of pericardium and large vessels without symptoms referable to the heart and although both kidneys were riddled with metastases there were no changes in the urine or renal function. Hemiplegia due to cortical metastases cleared up before death with the symptomatology of an arrested cerebral hemorrhage.

The case was that of a man 44 years old, who enjoyed good health up to about six months before he came under observation, that is, until November, 1923.

Family History: His father died of tuberculosis, and his mother and two sisters are living and well.

Present History: His first symptoms in November were of a cough with a return of the cold in December, and in March and April he felt run down. At that time he had an x -ray picture which showed the beginning of the process. He came to the Fifth Avenue Hospital in May, on the service of Dr. C. F. Tenney, through whose courtesy the case is shown. His chief complaint was a persistent cough and the raising of a considerable amount of sputum, largely purulent. He remained in the Hospital until July, and went home for a week, to return on August 5. The symptoms he presented while in the Hospital were of changes in the left lung and persistent cough. He was subjected

* Presented November 13, 1924.

to puncture of the left pleural cavity, with the withdrawal of sterile fluid at first, which later contained pus and *Staphylococcus aureus*. On the basis of this an incision was made, exposing the lung and leading into an abscess cavity which contained a fair amount of pus. The cavity was drained. The wall of the cavity was composed of dense fibrous tissue. This drainage was kept up until the patient left the Hospital and at the time of the autopsy the wound had pretty well healed. There was practically no increase in temperature. The red cells were normal at first, gradually falling to 3,500,000. There was a moderate leucocytosis with no increase of the polynuclears. Urine examinations were negative except for a trace of albumin from time to time and a few hyaline casts. The blood chemistry in May was normal. The main symptoms in the Hospital were persistent cough and loss of strength and weight. In June there was a slight convulsive twitching of his face, followed by paralysis of the right hand and the right side of the face. This cleared up so that when the patient returned on the 18th of July there was mere loss of power without loss of sensation or paralysis.

Physical examination showed a change in voice and evidence of consolidation in the upper part of the inner portion of the left lung. The heart sounds were normal. The pulse rate at first was quite constant and did not indicate a cardiac disturbance. The x-ray picture first made in March showed evidence of some growth near the median line on the left side. This at subsequent examinations was shown to be growing rapidly and extending toward the left. The examinations were made by Dr. Lewis G. Cole, and a number of examinations showed that it was probably a tumor of the lung. At the time of the operation when the abscesses were found Dr. Cole still held the view that it was an abscess complicating a tumor. The material removed from the abscess did not show any tumor growth. It was merely broken down necrotic material mixed with inflammatory exudate.

The autopsy showed an emaciated man with evidence of an old operation on the left side and also a thickening of the sternal region. On opening the chest cavity there was found a growth which invaded the sternum and anterior chest wall with loss of practically the entire structure of the bone of the sternum.

The left pleural cavity was occupied by a protruding growth which extended from the median line outwards for 9 cm. where it fused with the lung and its adherent pleura. It had a vertical length of 10 cm. and was continuous at its lower border with the thickened pericardium. The visceral pericardium was studded with pale nodules 1 to 3 cm. in size, so that very little uninvaded heart muscle could be seen. On section the tumor had invaded the lung outwardly and posteriorly, so that there is a mere shell of lung tissue remaining above and at the side. The growth extended back, embracing the structures of the mediastinum and surrounding the left bronchus and aorta and pulmonary artery. It was composed of very dense pale tissue, and embedded in it were several pigmented nodules which appeared to be bronchial nodes. The nodules on the surface of the heart extended down to the muscle and in some places

were embedded in the heart muscle. The wall of the left ventricle was 4 cm. thick and the cavity very small. The aortic opening was surrounded by the tumor and the aorta from its commencement was surrounded by a rigid wall of tumor. The right ventricle was also contracted and the pulmonary artery was very narrow and surrounded by the tumor.

The right lung showed congestion and edema with encroachment by the new growth at the hilum. In the center of the tumor, at its left border, there was a broken-down area of abscess cavity. The tumor appeared to be one which had started in the left mediastinum and spread downwards over the heart and outwards into the lung.

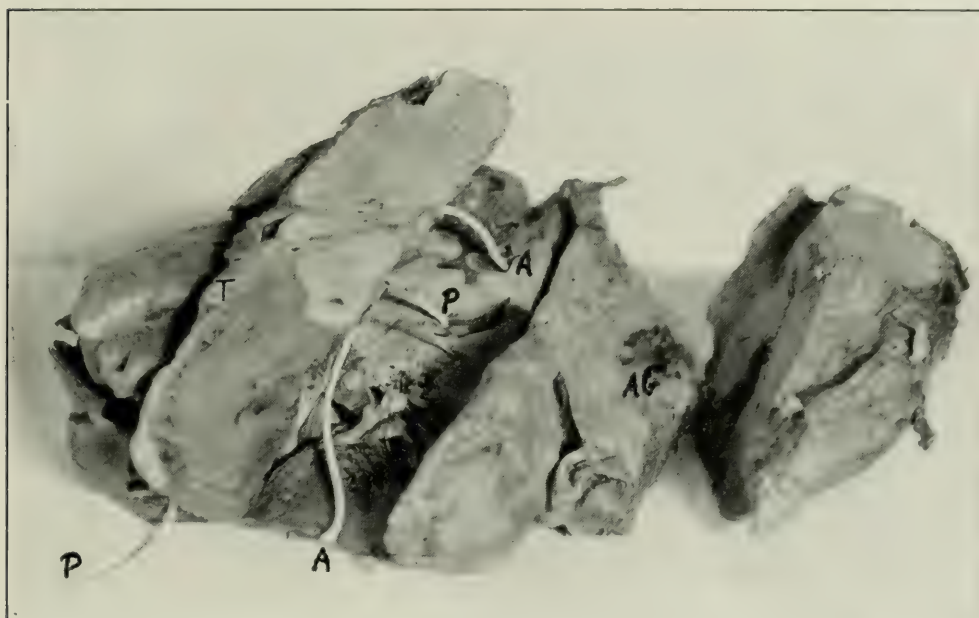


FIG. 1. F. A. H. Autopsy 91. Tumor of lung with heart laid open showing cavity of left ventricle with thickened wall and invasion of pericardium by tumor at T. The tumor is also shown encroaching upon the auricles and large vessels. White cord A.A. lies in cavity of left ventricle and passes through aorta. White cord P.P. passes through right ventricle and pulmonary artery. Both large vessels are encased in solid tumor growth. Ab, site of abscess in the tumor of the lung.

Further examination showed beside the invasion of the sternum extensive metastases of both kidneys and the retroperitoneal lymph nodes, and on opening the brain on the left side in the temporal region corresponding to the motor areas of the upper extremity and face there was a bulging of the cortex which proved to be a cyst containing clear fluid, so as to resemble an echinococcus cyst. This was 4 cm. in diameter and its wall was made up entirely of new growth.

Microscopical Examination: The growth in the lung shows nests of large

cells separated by narrow septa of stroma and giving the appearance of a squamous cell carcinoma. In the adjacent lung there are inflammatory changes of a chronic productive nature with increase of connective tissue.

Sections of the mediastinal nodes show invasion by the new growth with considerable necrosis.

The large bronchus is surrounded by new growth and has also invaded, the tumor extending through and replacing the lining epithelium at one point.



FIG. 2. F. A. H. Autopsy 91. Microphotograph showing squamous cell carcinoma in mucosa of large bronchus.

The aorta is surrounded by new growth just above the aortic cusps.

The pulmonary artery also passes through the solid growth.

The nodule in the tumor, thought to be a node, is apparently a vessel filled with necrotic tissue and portions of the new growth, *i.e.*, it is new growth in an organizing thrombus.

Sections from the kidney metastases show a fibrosis of the surrounding

stroma in contrast to the lesion in the brain, where the stroma is scanty with engorgement of its blood vessels.

The interesting features of the case in the first place are the lack of embarrassed heart action. The heart was entirely surrounded above and on all sides with new growth with a lessening in the size of the ventricles and auricles and there was a solid tumor through which the larger vessels were passing. In spite of this there was no abnormal heart action. The kidneys also showed no change as far as function was concerned. In the case of the cerebral symptoms there was apparently a paralysis in June with the symptoms described, followed by a clearing up of symptoms so that at the time of his death the patient had no distinct paralysis or sensory disturbance.

Carcinomas of the lung have been described as of three types, cylindrical cell, squamous cell and mixed cell carcinoma. In this case both the primary tumor and the metastases show a type that would place it with the squamous cell group. No evidence of keratinization was found in the sections. While there are various theories as to the source of these squamous cell growths, the view that they come from the epithelia of the bronchi by a process of metaplasia seems the most plausible. The progress of the tumor as studied by the *x*-ray indicates that it began in the mediastinal region; and the sections of a large bronchus show involvement of the whole thickness of its wall by nests of squamous epithelium, so that the process might well have begun here.

HODGKIN'S DISEASE OF THE SPLEEN *

LEON H. CORNWALL, M.D.

This spleen was removed at autopsy ten years ago but because of the meagerness of the clinical data I have never presented it to this Society before.

I offer it now as an example of primary Hodgkin's disease of the spleen.

The patient was a female, white, unmarried, and 29 years of age. I am unable to furnish any information concerning the duration of her illness and practically no clinical facts.

On September 11, 1914, she entered a hospital for the care of tuberculous cases complaining of malaise, loss of thirty pounds in three months, and a slight cough was said to have been present intermittently for one year. There was moderate hyperthermia, the temperature ranging between 99° and 101° F. during her stay in the hospital. While no clear account was obtained concerning the physical findings I was informed that a tentative diagnosis of pulmonary tuberculosis was made. Death occurred on September 24, 1924, and an autopsy was performed the same day.

The post-mortem findings were briefly as follows:

The development and nourishment were fair. There were no external scars nor deformities. Rigor mortis was present but easily broken.

The peritoneal cavity contained 500 c.c. of a clear serous fluid.

The intestines were free in the peritoneal cavity and the peritoneum was smooth and glistening. The appendix showed no gross lesions.

The liver extended four fingers below the free costal margin in the right mid-clavicular line.

The stomach was moderately distended with gas and extended three fingers breadth below the umbilicus.

Thorax: The thymus gland was replaced by thymic fat. The heart and lungs were normal in position. The mediastinal glands were not enlarged.

The left lung weighed 400 gm. It was free in the pleural cavity, which contained about 600 c.c. of clear fluid. Section disclosed a chronic passive congestion and edema.

The right lung weighed 590 gm. It was bound down by a few easily broken adhesions at the apex. On section it was salmon pink in color and edematous. There were a few areas of terminal broncho-pneumonia in the posterior and dependent portion.

The heart weighed 395 gm. It lay free in the pericardial cavity but the latter contained 600 c.c. of a clear amber-colored fluid. The orifices were normal in size and the valves all appeared thin, delicate and competent. The heart

* Presented November 13, 1924.

muscle was pale in color and flabby in consistency. The right ventricle measured 4 mm. and the left 13 mm. in thickness.

Abdomen: The liver weighed 1,800 gm. There was a moderate thickening of the capsule with a few linear scars on the inferior surface. There was distension of the sub-capsular lymphatics. Section disclosed rather pale tissue which was soft and friable on palpation. It was yellowish in color and with the exception of a few areas that had the mottled appearance of chronic passive congestion the liver gave the gross picture of parenchymatous degeneration.

The gall bladder contained about 2 oz. of bile of a normal color. The mucous membrane was normal in appearance and no calculi were present.

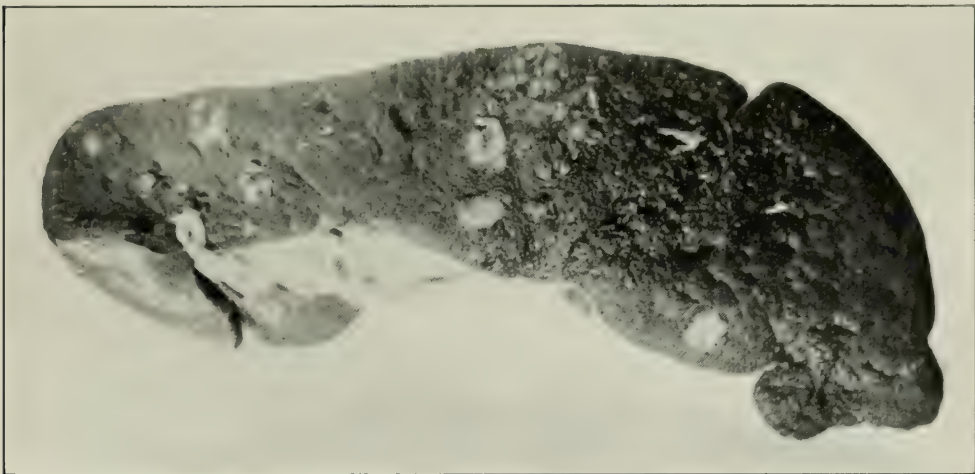


FIG. 1. Section of the spleen showing the gross appearance of the Hodgkin's nodules

The pancreas weighed 130 gm., but presented no gross pathological change. There were several hyperplastic peripancreatic lymph glands, one being about the size of a walnut and the others the size of a pea.

The left kidney weighed 225 gm. The capsule stripped readily. The cortex was pale and moderately swollen. The consistency was normal. The cortical markings were indistinct and the picture was that of anemia and cloudy swelling.

The right kidney weighed 250 gm. and did not differ from its fellow on the left.

The stomach contained 400 c.c. of semi-digested food material. The normal rugæ of the mucous membrane were lost and there was a moderate degree of post-mortem digestion of the mucous membrane.

The right fallopian tube was dilated at its distal extremity and the fimbriated extremities of both tubes were adherent to the ovaries. The right ovary was moderately enlarged and contained several small cysts. The left ovary was normal in size but on section disclosed several small cysts.

The bladder was normal.

The aorta was normal in elasticity and showed no gross pathologic change.

The spleen weighed 450 gm. On transection it was deep red in color, and scattered through the splenic pulp were many nodular areas varying from the size of a millet seed to the size of a walnut. These were yellowish-white in color and appeared grossly to be fairly well circumscribed. Each one of the larger nodules gave the appearance of being composed of several smaller nodules. The gross appearance resembled that of metastatic neoplasm. The splenic pulp between these nodules was soft and easily scraped off on the edge of the knife. There was one lymph gland at the hilus of the spleen about the size of a pea. At the time of the autopsy these areas were considered as probable metastatic neoplasms but no primary growth could be identified.

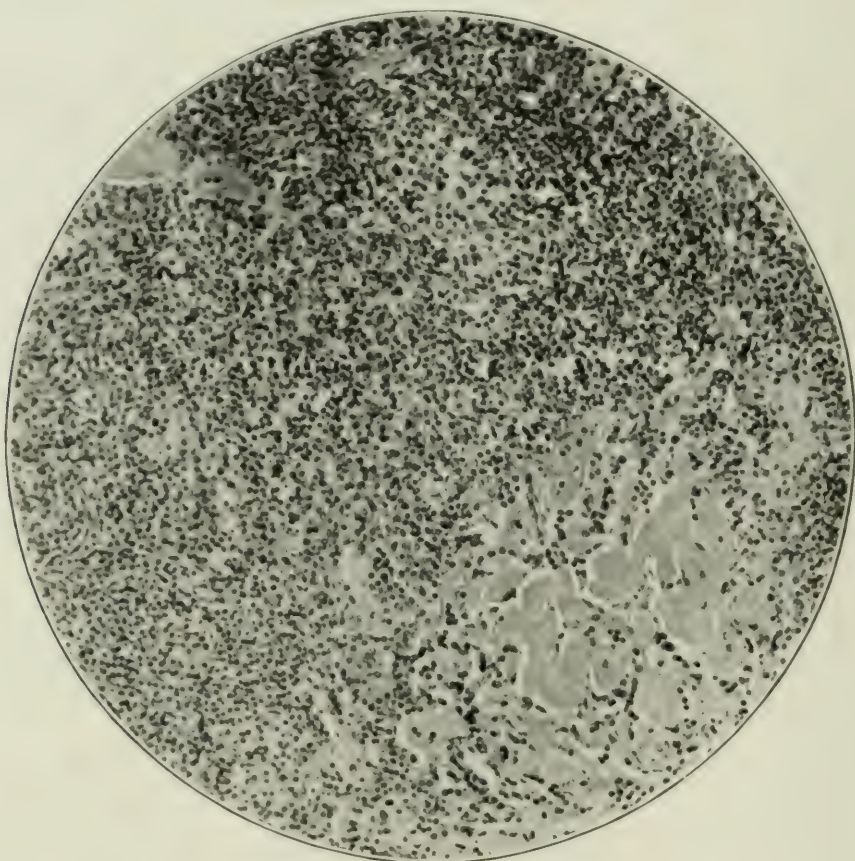


FIG. 2. Low power photomicrograph of the spleen showing an area of hyalinization with hypoplasia of lymphoid elements and hyperplasia of the endothelial cells.

There were no enlargements of the cervical, axillary, or inguinal lymph nodes. The mesenteric and retroperitoneal lymph nodes were not enlarged except those around the head of the pancreas and at the hilus of the spleen as previously noted.

Microscopical Examination: Spleen: The capsule was thickened and there

was an accentuation of the trabeculae of the organ. In a few areas the capsule was infiltrated with lymphoid tissue. The lymphoid elements of the spleen were greatly diminished in number, the nodules in many places consisting merely of narrow zones around the smaller blood vessels. Between these remnants of the lymphoid nodules were large areas in which the normal splenic tissue was replaced by areas of hyalinization. The smaller arterioles showed productive endarteritis, many of them being entirely occluded. The larger branches of

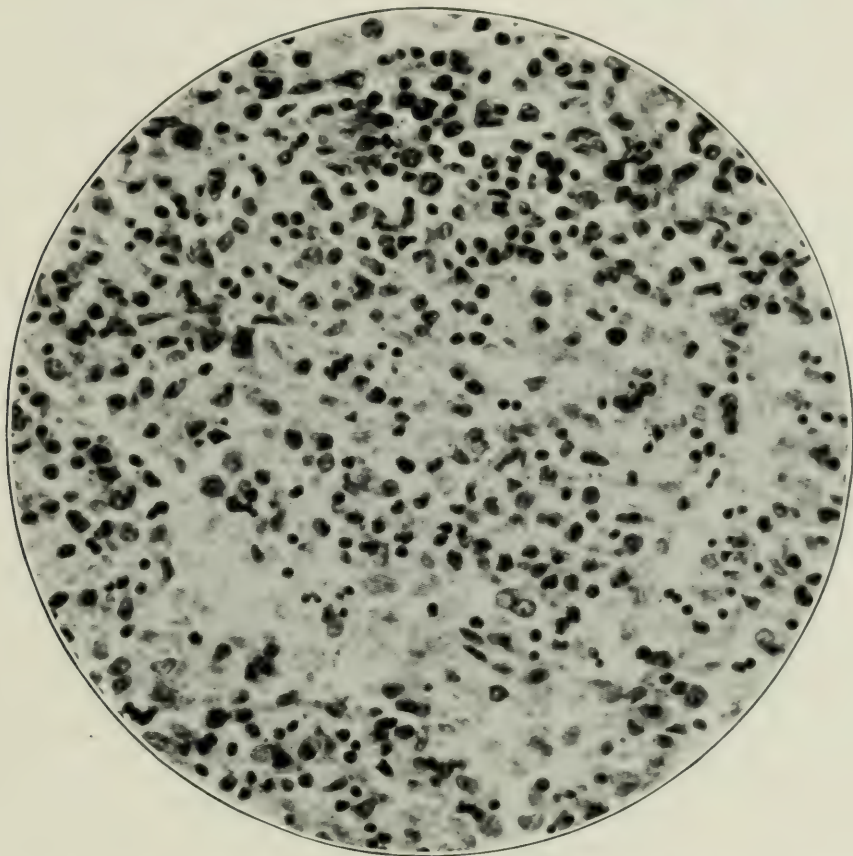


FIG. 3. High power photomicrograph through one of the nodules of the spleen

the splenic artery were surrounded by areas of fibrosis. There was a proliferation of the connective tissue cells of the reticulum and there was hyperplasia of the endothelial cells among which were scattered plasma cells. Blood pigment was abundant. No eosinophiles were seen. There were many large irregular endothelial cells with relatively large multilobulated nuclei which stained fairly deeply with nuclear stains. Some of the nuclei contained from 1 to 3 nucleoli. Whereas the nuclei of the endothelial cells were large and irregular in form the multiple nuclei that are so characteristic of the cells described by Sternberg were not frequent.

Lymph Nodes: The peripancreatic lymph nodes showed inflammatory

edema. The lymph cords were separated by wide clear spaces. The endothelial cells lining the reticulum, blood vessels, and lymph spaces were distinctly swollen. A few endothelial cells had wandered out into the cords of lymphoid tissue. The lymphoid elements did not show hypoplasia to the same degree that was noted in the spleen. There were a few areas consisting of pinkish stained hyalin-like ground substance containing numerous faintly stained round, oval, and elongated nuclei, some of which were vesicular. There appeared to be an actual increase in number of the blood capillaries and lymph sinuses all

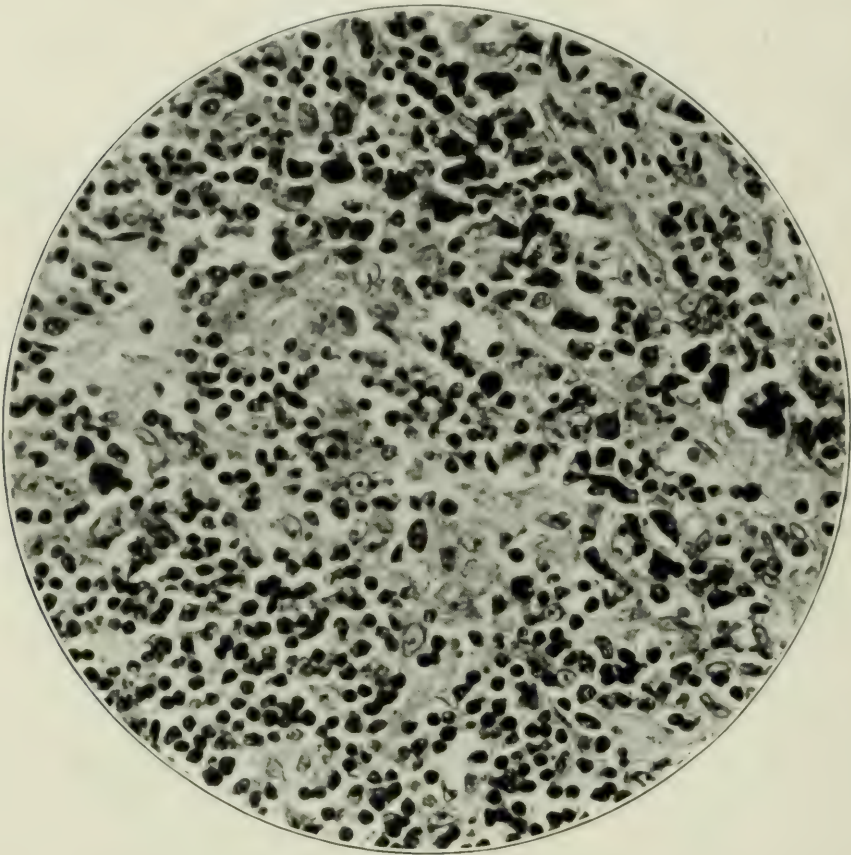


FIG. 4. High power photomicrograph of the lymph node at the hilus of the spleen

of which showed a distinct swelling of the lining endothelium. Scattered through the pulp tissue and surrounded by clear spaces there were a few large irregularly shaped cells with large lobulated nuclei that occupied almost the whole of the cell body. In only a few of these cells could more than one nucleus be distinguished and even in these cases one gained the impression that the nuclei were lobulated rather than multiple. Many of the lymph channels were filled with a hyalin substance containing a delicate fibrillar material of web-like character that stained deeply with eosin. The lymph nodes showed no fibrosis nor were any eosinophiles discovered.

The liver showed congestion of the central veins of the lobules with acute cloudy swelling of liver cells and areas of focal necrosis. There were a few small foci consisting of from 10 to 20 cells of lymphoid and plasma cell type situated within the liver lobules.

No bone marrow was obtained because of restrictions that were placed upon the autopsy.

On the macroscopic and microscopic appearance of the splenic lesions together with the absence of any enlargement of the cervical, axillary, inguinal and thoracic lymph nodes and the meagerness of the pathological changes in the few abdominal lymph nodes, the diagnosis of primary Hodgkin's disease of the spleen was made.

The absence of more complete clinical data is to be regretted and impairs the value of this presentation but inspection of the gross specimen and the microscopical sections will, I believe, convince you of the correctness of the diagnosis. The presentation may be of special value to younger pathologists because of the resemblance of the lesions to neoplasm. At the time that I autopsied this case my diagnosis was metastatic neoplasm with an undiscovered primary focus. The diagnosis of Hodgkin's disease was not made until after the microscopical examination.

RHEUMATIC CARDITIS WITH PREDOMINANT INVOLVEMENT AND CALCIFICATION OF THE LEFT AURICLE

REPORT OF A CASE *

HAROLD J. STEWART, M.D., AND ARNOLD BRANCH, M.D.

*(From the Hospital of the Rockefeller Institute for Medical Research,
New York City)*

We desire to report the following case of rheumatic heart disease, particularly to emphasize the occurrence of involvement of the left auricle, if submiliary nodules of the Aschoff body type are accepted as evidence of this infection. The case is further

* Presented November 13, 1924.

interesting on account of the calcific nodules found in the left auricular endocardium, in the left ventricular myocardium, and at the base and in the substance of the mitral valve.

MacCallum¹ has recently called attention to the involvement of the left auricle in rheumatic hearts, but we have been able to find in the literature only two cases resembling ours, and in both instances they were considered as being probably inflammatory in origin. The first heart was demonstrated by Claude and Levaditi² to the Anatomical Society of Paris in 1898, *i.e.*, before the Aschoff body had been described. Neither age, sex, nor clinical history was given. The gross description of small, irregular ulcerations with calcareous bases scattered over the endocardium of the left auricle, especially numerous in the neighborhood of the mitral orifice and extending up to the orifices of the pulmonary veins, closely resembles the case here described. In the microscopic description particular attention is paid to endarteritis involving the capillaries of the endocardium, myocardium and pericardium. The capillaries were surrounded by round cells of the type of embryonic connective tissue cells. These observers attributed the lesion to an inflammatory condition and suggested a possible explanation of the ulceration and degeneration to the condition of the vessels, some of which were partly closed. The other case was reported in 1906 by Lazarus and Davidsohn³ and concerns a girl of nineteen who died of sarcoma of the dura mater. She gave no history of rheumatic fever. At autopsy the valves and pericardial cavity showed no lesions, but the endocardium of the left auricle was extensively calcified. Microscopically they noted that the calcified plaques were in the subendocardial tissue, but that the thickening of the endocardium of the left auricle differed from that normally seen in an arteriosclerotic lesion as the *connective tissue cells were increased in number, containing many nuclei, and tended to group themselves in isolated patches near the myocardium.* We are left in doubt as to whether these were true Aschoff bodies.

SUMMARY OF CASE REPORT

M. L., female, age sixteen years, was admitted to the hospital January 2, 1923, and died January 3, 1923. The patient first came under observation in May, 1913, that is to say, ten years before admission, when she was six years old. An older sister has also been a cardiac patient in this hospital. The patient had measles at two and a half years of age; tonsillitis frequently in her fifth year, but had had no attacks for one year before the first admission. She had diphtheria in her fourth year and was treated with antitoxin. It is known that she had "heart trouble" for one year before 1913. The patient came to the hospital at that time because of fever and precordial pain of one week's duration. Examination then showed generalized cyanosis, enlarged tonsils, enlarged liver and palpable spleen. There was no edema. There was a marked bulge of the precordium and a heave with each heart beat. The heart was enlarged to the left. A systolic murmur was heard over the whole precordium, but was best heard at the apex. The cardiac rhythm was regular and the rate was rapid. While in the hospital the patient had vague rheumatic pains in the left knee, with slight tenderness and local heat, and a slight rise in temperature. Her tonsils were removed under chloroform anesthesia. During observation in the hospital an apical diastolic murmur appeared. The patient was given tincture of digitalis, the cardiac rate was reduced, and she was discharged improved after being in the hospital for two months. The patient was seen at frequent intervals from 1913 to 1916, was kept on digitalis and was able to go to school. In 1915 a systolic and diastolic thrill appeared at the apex. In February, 1916, the patient was readmitted because of precordial pain, dyspnea and slight fever. The cardiac enlargement had increased since the previous admission. At this time R_2 and R_3 in the electrocardiograms had become higher and S_2 and S_3 which had been present had disappeared. During this admission digipuratum was substituted for the tincture of digitalis. She was in the hospital for four months and was discharged improved.

The patient was readmitted in October, 1917, for one week, and it was found that the cardiac mechanism had changed to auricular fibrillation. Digitalis promptly reduced the rate. In January, 1918, the patient was readmitted for two months, when edema was observed for the first time. The patient was readmitted in September, 1922, with outspoken cardiac decompensation and remained in the hospital for four months. During this admission she had at intervals a rise in temperature, with a slight leucocytosis. There were no petechial spots, and repeated blood cultures showed no bacterial growth. There were no joint symptoms. At one time a doubtful rheumatic nodule was discovered at the right elbow. During the early part of this admission the cardiac rate could be controlled satisfactorily with digitan (Merck), but the edema persisted. The figures for kidney function tests were within normal limits. Diuretin and theocin increased the urinary output and decreased the edema, although at no time was the patient entirely free of edema. The patient was subjectively disturbed by a large number of ventricular premature contractions

and she was given a total of 0.3 gm. of quinidine sulphate, in an attempt to control the premature contractions. The cardiac rate immediately became rapid and it was not possible to reduce it to its former low level, although larger doses of digitan were given and the electrocardiograms showed a digitalis effect. The patient was discharged, against advice, unimproved.

Two weeks later she was readmitted with extreme cardiac decompensation, became steadily worse and died the day following admission. On this admission the physical examination showed marked bulging deformity of the anterior chest wall, the heart enlarged both to the right and to the left, the rate diminished since the last admission, a diastolic thrill over the apex, the heart sounds loud, a loud systolic murmur at the apex replacing the first sound; and the second sound replaced by a diastolic rumble. The pulmonic and aortic sounds were rumbling in quality; the sounds over the pulmonic area were louder than over the aortic area.

Clinically we inclined to the belief that the patient had a long-standing mitral lesion and also an active rheumatic infection of the heart muscle because of the febrile periods with slight leucocytosis, and the presence of the doubtful rheumatic nodule. The absence of a positive blood culture and of embolic phenomena made the diagnosis of subacute bacterial endocarditis unlikely.

SUMMARY OF AUTOPSY FINDINGS

An autopsy was performed fourteen hours post mortem.

Anatomical Diagnosis: Rheumatic pancarditis, fibrous pericarditis, chronic valvular disease (mitral and tricuspid), chronic mural endocarditis with calcification, chronic myocarditis with calcification, cardiac hypertrophy and dilatation, perihepatitis and perisplenitis, cirrhosis of liver, advanced passive congestion of organs, ascites, edema, atheroma of aorta and pulmonary artery, fatty infiltration of pancreas.

Gross Examination: The body is that of an emaciated girl, 150 cm. long, with brownish, muddy skin and noticeable chest deformity. External examination reveals no other positive signs.

Thorax: The precordial area at its widest point measures 18.5 cm. and occupies the whole transverse diameter of the chest. There is little fibrous anterior mediastinitis. There are a few fibrous adhesions between parietal pericardium, lung and chest wall.

The *lungs* show brown induration.

The parietal pericardium is markedly adherent to the visceral over the surface of the ventricles anteriorly and over the whole left auricle (Fig. 1). The posterior, inferior, and lateral surfaces of the ventricles and the whole right auricle are free of adhesions (Fig. 1). The orifices of the pulmonary veins are pulled over to lie on the anterior surface of the left auricle, well in front of the usual lateral incision (Fig. 1).

The *heart* weighs 830 gm. with the pericardium; the musculature is firm and a pinkish brown color. The transverse diameter measures 14 cm.

The *right ventricle* is somewhat dilated at the base, the wall measures 8 mm. Its endocardium is intact.

The *right auricle* is tremendously dilated, tense, and after opening readily admits the closed fist. The endocardial lining is thin and smooth. The wall, except in the appendix, is very much thinned out almost to the thickness of

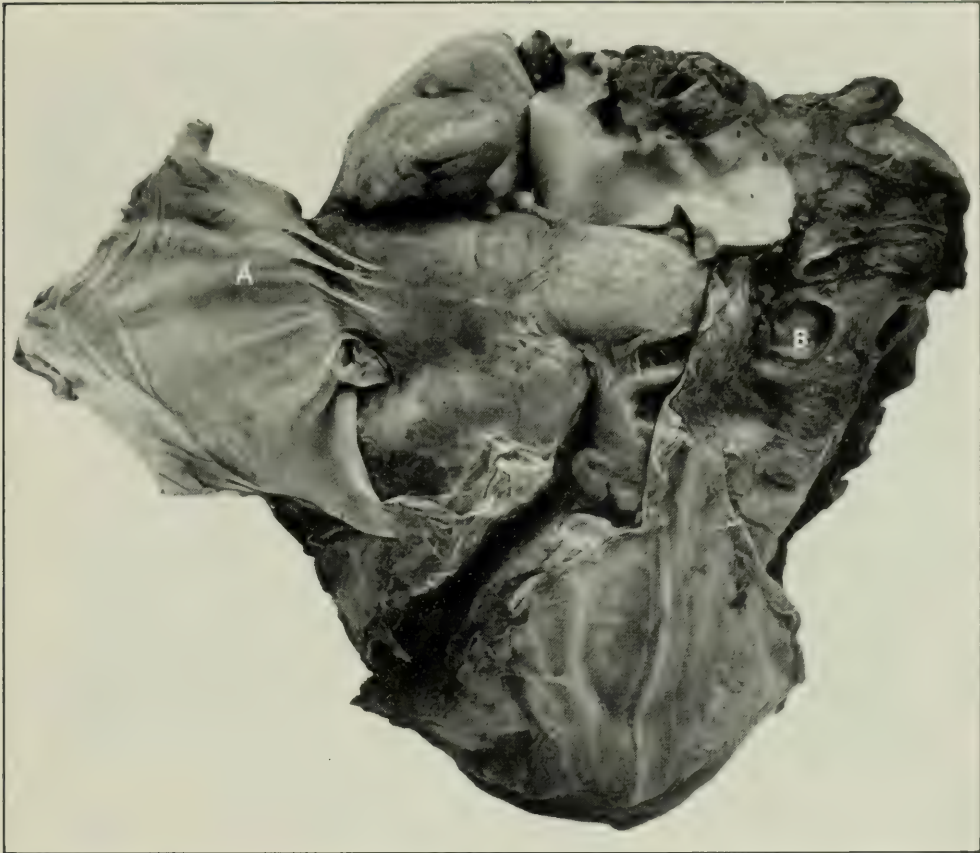


FIG. 1. Photograph of the anterior surface of the heart. *A*, the adherent pericardium. *B*, the unusual site of the orifices of the pulmonary veins.

parchment paper. The foramen ovale is completely closed and the coronary sinus admits the forefinger to the first joint. The orifice of the inferior vena cava is very wide and practically admits a 25 cent piece.

The *left ventricle* is hardly enlarged; the wall measures 13 mm. On sectioning the lateral wall, well embedded in the musculature, a small calcareous mass is cut into, round in outline, measuring 6 mm. in diameter and sharply defined from the surrounding tissue (Fig. 2). A similar small nodule is seen in the adjoining muscle just under the endocardium through which it shows. Neither of these nodules is apparent on the external surface.

The *left auricle* is markedly dilated and admits the closed fist after opening. Its walls are thickened, tough and firm. The endocardium is opaque, thickened throughout and studded with many calcareous plaques. Over most of these there is no endocardium and they form irregular ulcers with rough yellow bases. When sectioned the calcification is seen to be in the subendocardial tissue. They occur especially on the anterior surface around the orifices



FIG. 2. Photograph of the opened left side of the heart. *A*, the calcified area in the myocardium of the left ventricle. *B*, the calcified ulcers in the endocardium of the left auricle. *C*, the subendocardial calcified nodules on the mitral valve.

of the pulmonary veins, at the orifice of the auricular appendix, and above the base of the aortic cusp of the mitral valve. Quite distinct plaques occur, however, at greater intervals on the posterior and medial surfaces, even as high as 8.5 cm. above the base of the mitral valve, that is, almost in the extreme vault (Fig. 2). Scarred areas occur between the plaques where these are in close proximity with one another. The pulmonary veins at their insertion are not thickened.

The *mitral valve* readily admits two fingers and when opened measures 12 cm. The cusps are thickened and "rolled over" along the free edge and the ring slightly fixed and calcified. Three small subendocardial nodules, quite smooth on the auricular surface and resembling large verrucae when viewed from the ventricular surface (Fig. 3), are situated on the aortic cusp and one such on the non-aortic cusp some distance from the free edge and at the attachment of a chorda tendinea. A pea-sized calcareous subendocardial mass is noted embedded in the subendocardial tissue of the interventricular septum at the base of the lateral cusp. The chordæ themselves are thickened but not cemented together nor are they ruptured.



FIG. 3. Photograph of the ventricular surface of the aortic cusp of the mitral valve. *A*, *A*¹, *A*², the verrucose-like deposits. *B*, the subendocardial calcified nodule.

The *tricuspid valve* admits three fingers and measures, opened, 15.5 cm. It is thickened only at the edge. Two subendocardial small calcareous nodes are present near the base, one on the anterior and one on the posterior cusp.

The *aortic valve* measures 5 cm. opened. The corpora arantii are large. The *pulmonary valve* has slightly thickened edges and when opened measures 6.8 cm. The aorta is small and there are a few yellow thickened patches. The *pulmonary artery* at its origin shows more thickening than the aorta. The *coronary arteries* show but very few small yellow plaques, these being more marked in the anterior branch near its origin.

The *spleen* is firm and small. On section it is dark red, trabeculae are well seen, the corpuscles are not prominent and no infarcts are present.

Kidneys: There is one small, sunken area on the surface of the left kidney, otherwise they show no evident change.

Liver: There is typical "nut-meg" appearance with fibrous scars.

Microscopic Examination: Heart: Submiliary nodules are seen in the mural subendocardial tissue of all chambers but especially in that of the left auricle and ventricle. They occur also in numbers at the base of the non-aortic cusp of the mitral valve extending up to the left auricle, at the junction of the chordae tendineae and left anterior papillary muscle and one in the pericardium. The following is a composite description of such nodules in the subendocardial tissue of the left auricle: their situation is in the deeper subendocardial tissue

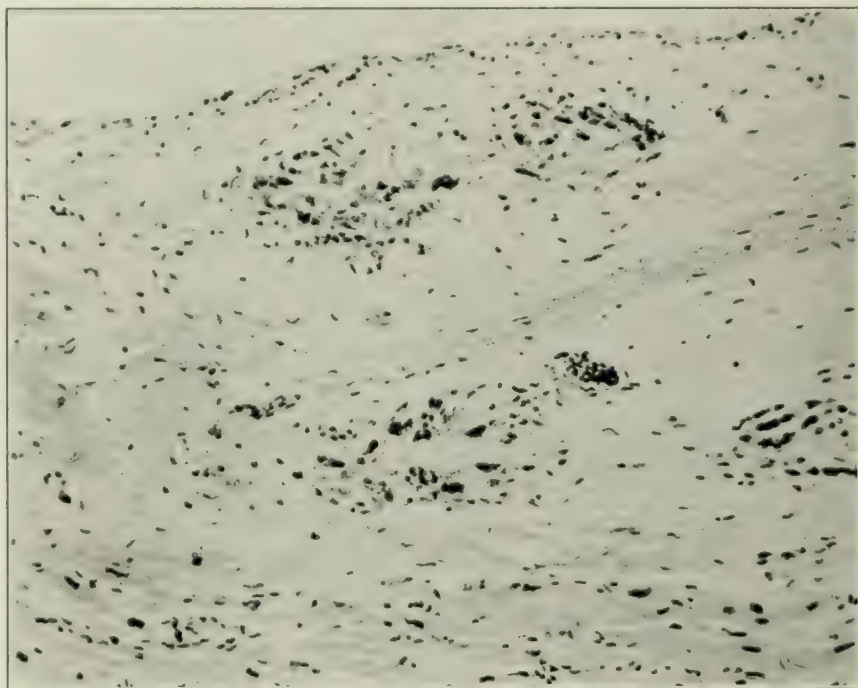


FIG. 4. Microphotograph of Aschoff bodies in the endocardium of the left ventricle.

adjoining the muscle fibers; they are not definitely perivascular but contiguous capillaries are numerous and show marked endothelial proliferation. They are discrete and easily differentiated from the surrounding tissue. Each nodule is composed of loosely arranged, large, pale staining cells, with large vesicular nuclei, the chromatin of which is as a rule collected into one or more clumps with fine lateral processes resembling burrs; occasionally the chromatin arrangement is in the form of a spirochete or centipede. The number of cells in single sections of an individual nodule varies between ten and twenty-five. Multinucleated cells with two, three or four nuclei are the noticeable feature. The center of the nodule is frequently acellular, structureless and stains poorly with eosin; the periphery fades inconspicuously into the surrounding tissue, or

there may be a narrow, incomplete zone of lymphocytes. The typical cells are round, oblong or elliptical; some show processes. They stain a bright pink with methyl green pylonin. One has little hesistancy in calling such structures Aschoff bodies (Figs. 4, 5, 6).

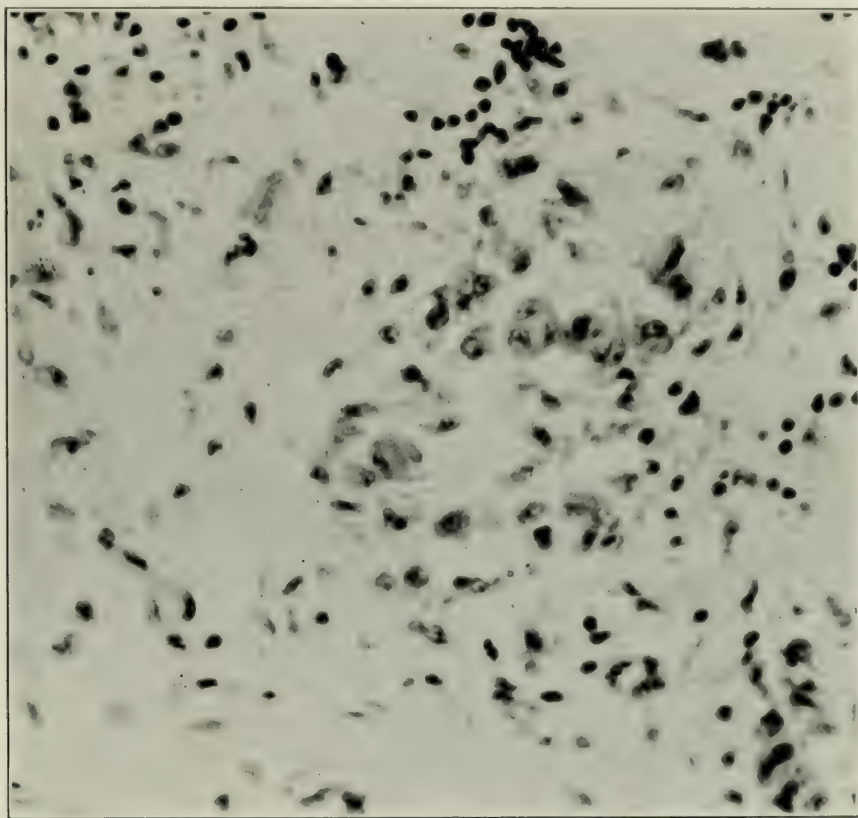


FIG. 5. Microphotograph of Aschoff bodies from the base of the non-aortic cusp of the mitral valve.

Left Auricle: The endocardium throughout shows fibrous thickening and this is accentuated in local areas, thus causing an irregularity of the surface. In some of these localized thickenings hyaline changes have occurred and in others there are calcified deposits and more extensive degeneration. Only occasionally are small degenerated areas seen deeper in the endocardium. Over some of these degenerated foci the surface endothelium is lost, resulting in superficial ulcers, the bases of which are formed of calcareous and hyaline material. Over others the endothelium is still intact (Fig. 7). Portions of the calcified areas in the auricle examined microscopically showed an amorphous structure, but on addition of strong sulphuric acid gas was evolved and needle-like crystals of calcium sulphate were formed. Scrapings gave positive qualitative tests for calcium, phosphates and carbonates. In some areas there is diffuse but scanty infiltration with small round cells. Small capillaries with proliferating endothelium are noted but no occlusion of their lumina. No

Aschoff bodies occur in contact with these degenerated areas but they are found in considerable numbers at the base of the auricle above the mitral valve. The myocardium shows old fibrous scars and only one Aschoff body was found. The striations in the muscle fibers are distinct; some fat granules are present in Sudan preparations. The muscle nuclei appear elongated and their chromatin tends to take the shape of a rosary with lateral off-shoots. This type of nucleus is commonest in the definitely degenerating fibers. The blood vessels are sparse and show no degenerative or thrombotic lesions.

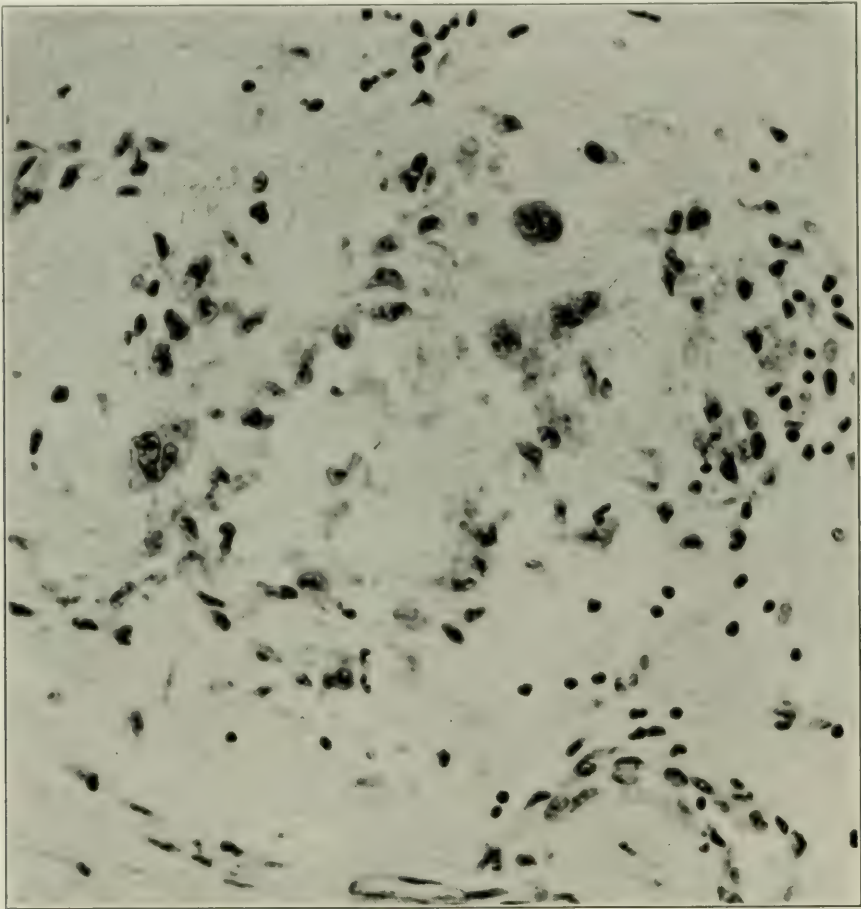


FIG. 6. Microphotograph of Aschoff body in the endocardium of the left auricle just above the non-aortic cusp of the mitral valve.

Left Ventricle: Fibrous scarring and old infarcted areas are quite frequent. Aschoff bodies are rare, except in the subendocardial tissue. There are occasional small areas of polymorphonuclear infiltration. The muscle fibers are relatively well preserved, except in the calcified zone, and little fat is present. One area of degenerated tissue is seen in the myocardium surrounded by a zone of fibrous tissue. No muscle cells are present here, but fibrous tissue strands divide the area into compartments filled with hyaline material and calcium.

A similar area is noted just below the endocardium and extending into the muscle and presenting a similar picture with a few "foreign body cells" at the periphery. Aschoff bodies are quite numerous in the subendocardial tissue of the lateral wall and the papillary muscles contiguous to this nodule.

Right Ventricle: Scarred areas, small exudative foci (Fig. 8) and Aschoff bodies are seen occasionally.

Right Auricle: Fat in the muscle occurs in some quantity; scarring is present but not marked; Aschoff bodies are sparse and the endocardium not thickened.

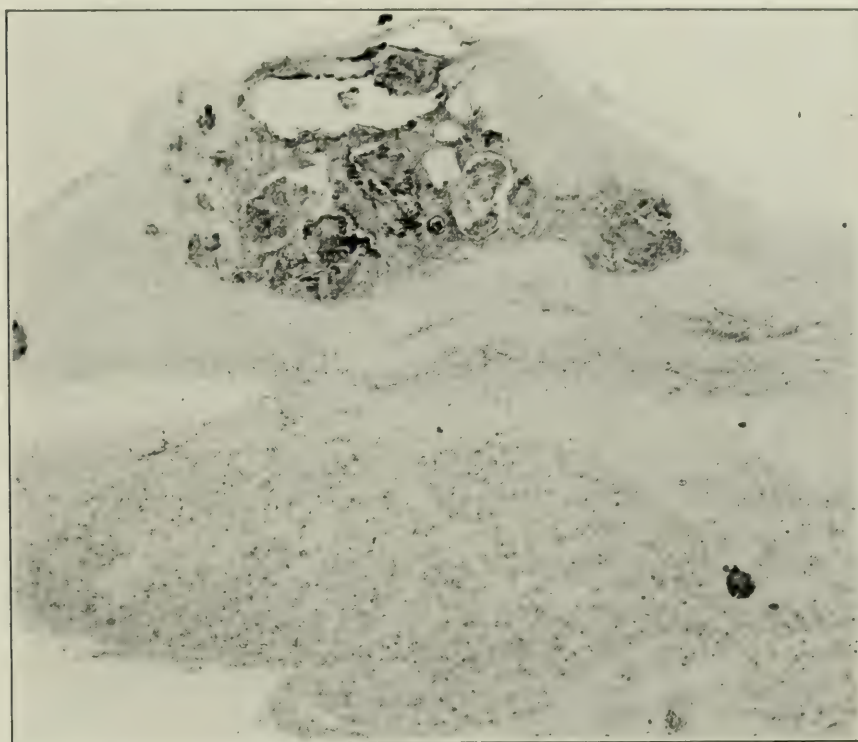


FIG. 7. Microphotograph of a calcified area in the endocardium of the left auricle.

Mitral Valve: No recent vegetations are present. The *aortic cusp* is thickened and blood vessels are seen surrounded by lymphocytic infiltration. Three calcareous nodules are embedded in the valve substance some distance from the free edge and at the attachment of the chordæ. They are situated deep in the valve substance and are made up of hyaline and calcareous clumps of degenerated tissue. They form definite elevations on both the auricular and ventricular surfaces of the valve but nowhere have they broken through to the auricular surface (Fig. 9). Two of these, however, are not covered on their ventricular surface by valve tissue so that they form the "verrucous-like" deposits seen grossly. They contain no recognizable cells, fibrin or platelets but are composed of hyaline and calcareous tissue. The change here

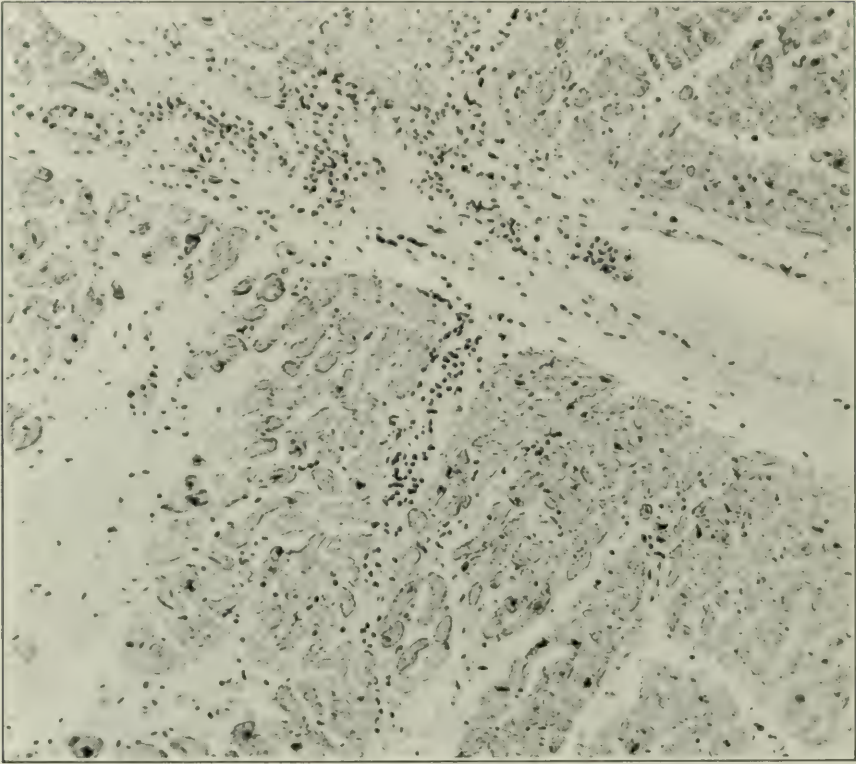


FIG. 8. Microphotograph of an area of small round cell infiltration and of scarring in the myocardium of the right ventricle.

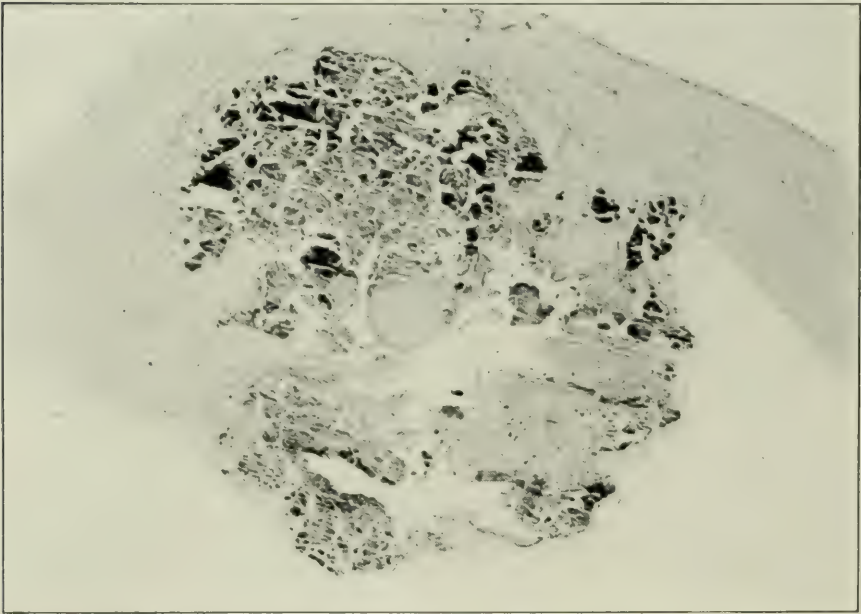


FIG. 9. Microphotograph of the calcified area and verrucose-like deposit in the aortic cusp of the mitral valve.

noted closely resembles that seen in the myocardium of the left ventricle, in the endocardium of the left auricle and at the base of the non-aortic cusp of the mitral valve and the process in every case simulates atherosclerotic degeneration. No organisms are seen in Gram's stain. In Von Kossa's calcium stain only parts of the material stain black with silver nitrate. The vessels in the valve near these areas are thickened but no endothelial proliferation or degeneration is noted. One Aschoff body is present in the endocardium at the junction of the papillary muscle and a chorda tendinea; the papillary muscle is scarred. At the base of the *lateral* cusp, including the valve tissue proper, are a row of isolated Aschoff bodies similar to those in the auricular endocardium. Situated subendocardially at the junction of the valve with the ventricular muscle is quite a large calcareous mass resembling those seen in the myocardium of the left ventricle but containing more calcium and less hyaline material.

The *tricuspid valve*: The calcareous nodule was not sectioned but sections of the other parts show lymphocytic infiltrations around vessels at the attachment of chordæ. In the ventricular musculature at the base there is a small focus of polymorphonuclear cells.

The *kidneys* show one small non-inflammatory infarct, with thickening of Bowman's capsule and occasional hyaline glomeruli, but no evidence of glomerular embolic lesions.

A description of the other organs is omitted for no information relevant to this disease is gained from their study.

SUMMARY AND DISCUSSION

One may with advantage briefly summarize the evidence at hand and emphasize the outstanding features brought to light in this case with a view to attempting its classification. These items to be considered are:

1. A clinical history of rheumatism and cardiac disease and fibrillation of ten years' duration.
2. Negative blood culture in life and at autopsy.
3. The absence of embolic phenomena clinically.
4. The presence of a doubtful rheumatic subcutaneous nodule.
5. The presence of adherent pericarditis.
6. The existence of many subendocardial Aschoff bodies.
7. No fresh vegetations were seen but there were slight chronic endocardial lesions of the mitral valve and tricuspid valves.
8. There was extensive involvement and calcification of the endocardium of the left auricle.
9. Marked lesions of the chordæ tendineæ were absent.

10. Focal exudative myocardial lesions and old scars were numerous.

11. The spleen was small.

12. One small healed bland infarct of the kidney was discovered but no focal glomerular lesions.

In Libman's ⁴ classification such a case of chronic endocarditis may be described as rheumatic, a healed example of the subacute bacterial variety, a mixed infection of these two forms or syphilitic. Of the other form, the indeterminate, not enough is known to warrant our including this case in that group; the acute forms, unlike this case, seldom heal. There is no evidence of the existence of syphilis, so that there are left for discussion rheumatic fever, subacute bacterial endocarditis, or a mixture of both forms. We accept the Aschoff body as evidence of rheumatic infection so that the question resolves itself into deciding whether an infection of this nature explains the whole picture or whether the healed form of subacute bacterial infection must also be considered. The only evidences in favor of the latter view are the site of the lesions in the left auricle and those on the mitral valve at its junction with the chordæ, whereas the evidences against it are the clinical course, absence of positive blood cultures, embolic phenomena and enlarged spleen and but slight involvement of the mitral valve. On the other hand, the clinical course suggests a rheumatic etiology as do also the Aschoff bodies, the adherent pericardium and the involvement of the mitral and tricuspid valves. We do not consider that the extensive involvement of the left auricle is against this theory since MacCallum ¹ has emphasized the presence of this type of lesion in rheumatism, nor are the focal exudative lesions which have been observed in this disease by Fahr, ⁵ nor the calcification which has been found by Bramwell, ⁶ Thalheimer and Rothschild ⁷ and others in rheumatic hearts.

We think that the pathological lesions in this case are due to active and healed inflammatory processes, perhaps unusual, and that the etiological agent is a recurrent rheumatic infection.

The fact should be emphasized that this case is not one of so-

called chronic valvular disease, as the valves were all relatively healthy, but rather must be considered as a case of chronic disease of the left auricle.

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Discussion:

DR. WOOD: Were Aschoff bodies demonstrated elsewhere than in the heart itself?

DR. BRANCH: No; they were not found elsewhere.

CONGENITAL OVARIAN CYST *

ALFRED PLAUT, M.D.

The patient (Record No. 15,478; pathological No. 24,830) was born at the normal end of the third pregnancy. The delivery was normal, as was the placenta. The child was cyanotic; its breathing was very poor; it died after fifteen hours in spite of all efforts. The autopsy showed severe jaundice, with many small hemorrhages in the serous coats. The liver was enlarged, weighing 172 gm. instead of 120. The spleen was also enlarged (27 gm. instead of 9). There was no perisplenitis. No spirochetæ could be found in the abdominal organs, either in the dark field examination or by the Levaditi staining. There was no osteochondritis.

One ovary was normal. On the other side, instead of the ovary, a thin-walled, ball-shaped cyst was found, measuring 2 x 1.5 x 1.3 cm. In its wall narrow meshes of well-filled blood vessels are seen; the cyst wall is very thin, the contents water-like. The ligamentum ovarii forms a pedicle of the cyst. Before reaching the cyst wall it forms a cylindrical swelling which is 1 cm. long and 4 mm. thick; the other portions of the ligament have the thickness of the sol string of the violin. Two cm. from the connection with the ligament, the outside of the cyst wall shows a milky white nodule the size of a pepper grain.

The thin cyst wall is lined by a single layer of partly cylindrical and partly

* Presented November 13, 1924.

cuboidal cells. The internal parts of the stroma are formed by a few layers of dense connective tissue; the outer parts consist of loose meshes of connective tissue fibers in which blood vessels are found. The above-mentioned nodule is a small cyst situated in this outer layer; its epithelium is cylindrical throughout. Many of the cells suggest some stage of secretory activity; the lumen is filled with an homogeneous coagulated mass.

It would seem futile to enter upon a discussion as to which kind of cyst this may be. In order to state the presence or absence of an ovum the cyst must be embedded *in toto*, and serial sections must be made; this has not been done. I do not think that the differential diagnosis can be made with certainty, since cases are reported where a cyst had an ovum like a follicular cyst and had true ciliated epithelium, like a serous cystoma, at the same time. This does not sound so incredible when we consider that in some animals the granulosa cells are ciliated.

The few reports of similar cases which could be found in the literature do not throw much light upon the question of their origin. Von Franqué¹ gives a picture of the lining of a congenital ovarian cyst; it shows a single layer of cylindrical cells which apparently are only modified from the granulosa cells. If we attempt to explain the formation of these cysts corresponding to the ripening process of the follicle, then we must assume that ripening occurs in the fetal period. This has been observed not infrequently (for literature, see W. Nagel, in Bardeleben: *Handbuch der Anatomie des Menschen*, 1896). Aschoff states that follicle ripening begins in the eighth month of fetal life. But these follicles grow only to half the size of the normal.

The pathological process which leads to the accumulation of fluid in the follicle may begin in different ages of the follicle, and the final picture may vary correspondingly. But it can never be a lutein cyst, since complete ripening and rupture of the follicle never is found in the fetus. Furthermore let us consider that there seems to be an hormonal influence from the sexual apparatus of the mother upon the organs of the child, manifesting itself in hyperemia or even hemorrhage of the endometrium and in the swelling of the mammary gland. The conclusion is obvi-

ous that there may be a similar influence upon the ovary of the fetus. The fact that von Franqué found eight follicular cysts in the ovaries of a mature fetus seems to strengthen this view. In a second case of the same author² there was one cyst in each ovary and the pedicle of the left one was severed by twisting. A congenital ovarian cyst is mentioned the size of a hen's egg;³ and another one which filled the abdomen like ascites;⁴ it contained 300 c.c. of fluid. v. Winckel⁵ saw symmetrical ovarian cysts 1.5 cm. in diameter in a seven months' fetus.

There is no uniformity concerning the condition of the mothers. In the case reported to-night, the mother was healthy; most of the few records in the literature do not mention any maternal disease. In the case of the very large cyst the mother had hydramnios, but since the baby had no hydrops and no edema, I fail to find the connection between the ovarian cyst and the hydramnios.

In conclusion, I think in our case the origin from one of the frequently occurring glandular formations in the ovary is more probable than the origin from a follicle. A specimen which I observed a few days ago demonstrates how easily we may be mistaken in considering the origin of an ovarian cyst. It showed a small glandular duct with high cylindrical epithelium, and this duct was surrounded by the hyaline masses of a corpus candicans. If you imagine this glandular structure giving rise to a cystic formation, you will find the hyaline masses surrounding the cyst, and after the epithelium is flattened or destroyed, you can wrongly conclude that the cyst originated from a corpus luteum in its late stage (corpus candicans cyst).

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BILHARZIA IN THE APPENDIX *

ALFRED PLAUT, M.D.

The patient, F. T., colored, twenty-six years old, record No. 33,937, was operated upon for a gynecological condition. The appendix was taken out; it was thin, 7 cm. long; the serosa slightly injected. Otherwise there was nothing of particular interest about the gross appearance of the appendix. Microscopically however there was a very unusual finding. Many eggs of *Bilharzia* are found in all the layers of the appendix, and in the lumen also. Many of the eggs are very well preserved and in one of them the typical miracidium is found. Other eggs show all degrees of destruction and at many points only an onion shell-like structure of the surrounding tissue indicates that there has been an ovum which has been completely destroyed. Around some of the eggs accumulations of eosinophiles are found (there was no eosinophilia in the blood). At several points it seems doubtful whether we are observing a partly destroyed egg and the surrounding tissue reaction or whether we have to deal with a blood vessel. Probably both are true—eggs have been caught with their sharp spine in the wall of a small blood vessel and around them the tissue reaction occurred which led to the destruction of the ovum. Some tissue reaction is present around all the eggs found in the appendix. There seems to be no relation between the situation of the eggs and the direction of the muscle fibers. As far as the contents of the eggs are well enough preserved to judge, they all seem to be young developing embryos already. Giant cells do not play an important rôle in the surrounding tissue reaction. The hemorrhage which is found in several places may be attributed as well to the presence of *Trichocephalus dispar* or to the trauma of operation; one male *Trichocephalus* was found in the feces of the patient but no eggs of *Trichocephalus* could be detected. The condition of the shell of the eggs is especially interesting. It is rather astonishing that the tissue succeeds in destroying this substance which resists our strong reagents. Apparently this shell assumes occasionally elasticity since at several points the ends of broken shells are coiled up. The spine with its thick base is the most resistant part of the shell and in looking for the position of the spines it could be found that in the same slide, even in the same microscopical field, one egg has a spine at the pole while the other one shows a lateral spine. This observation adds further strength to the conception that it is impossible to differentiate two different kinds of *Bilharzia* according to the position of the spine in the eggs. In the literature the difficulty is mentioned of making sure about the spines in the shrunken eggs in the tissue. In the slides of this case the differentiation seemed easy; the spines remained fixed in the surrounding tissue while the other parts of the shell frequently are separated from the tissue by an artificial space due to shrinkage; second, extrinsic folds of the shell are not as sharp as the spines are; third, the spine is never formed by the whole thickness of the shell which certainly is the case

* Presented November 13, 1924.

with the folds, but at the base of the spine a fine line is seen, concave inwards; this is the inner outline of the shell.

The question arises if this patient who never has had any symptoms of bilharziosis may have *Bilharzia* in other organs also. Only the cervix was available; one calcified egg was found in it without tissue reaction and one of the onion shell structures which as the appendix shows indicate the previous site of an ovum. The cervix was dissolved in anti-formin, but no other eggs could be found. The patient made an uneventful recovery and left the hospital.

As mentioned before, this case again shows that a differentiation of *Bilharzia Mansoni* as a genus of its own characterized by the lateral position of the spine is not acceptable.

It is not particularly surprising that this patient had no history of bilharziosis; this seems to be very frequently the case. The other astonishing fact, that this appendix, which was filled with the eggs and the inflammatory products, appeared perfectly normal, is frequently found also. This patient must have been infected long ago, as the calcified egg in the cervix proves. I prefer not to commit myself in any attempt to guess at the age of the lesions in the appendix. I do not know either how far the infection had spread in the body of this woman. But even if the cervix had not been available for examination, or if its examination had been negative, I would not agree with the conception of an isolated *Bilharzia* infection in the appendix. There are reports in the literature with this title, but none of them proves that the other organs really were free from eggs (Crimp, Turner, Ferguson). The laparotomy which was done for another gynecological condition may have benefited the patient; in many cases a laparotomy has been done in intestinal bilharziosis and following the operation the patients improved unexpectedly. In some of these cases the large inflammatory masses were mistaken for inoperable carcinoma.

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AN UNUSUAL CASE OF TERTIARY SYPHILIS OF THE LIVER *

EVERETT N. WHITCOMB, M.D.

(From the Pathological Laboratories of Bellevue Hospital)

A housewife, twenty-six years of age, entered Bellevue Hospital, the 11th of October, 1924. The family history was negative. She was a drug addict taking approximately nine grains of heroin a day. She had been addicted to this for seven years.

The past history is negative except for constipation, a leucorrhœal discharge and a recent loss of twenty pounds in weight.

Owing to the patient's stuporous condition the history was obtained from the husband. He denied venereal infection. Later a visitor admitted personal knowledge of the patient's first husband and stated that the latter was syphilitic and had been taking treatments at the Lenox Hill Hospital.

The total duration of the illness about to be described was eleven days, terminating fatally on the fourth day in hospital.

One week before admission the patient complained of abdominal pain and vomited a slightly bile-stained fluid. Three proprietary cathartics were taken without effect. Milk of magnesia was followed by white stools and pains described as due to gas. Bicarbonate of soda was followed by vomiting. Two days later her husband noticed jaundice over the chest and face. Three or four days before admission the patient herself complained of an enlarging abdomen. On the day of entrance to hospital she became incontinent of urine and mentally queer. No history of arsphenamine administration or other anti-syphilitic treatment could be obtained on careful questioning.

On admission the patient was stuporous and irrational. At times through the course she became restless and required restraint. She was deeply jaundiced; breath had the odor of acetone; the abdomen was distended with edema of the wall. Liver dullness began at the sixth rib and extended to the costal margin. The splenic area was enlarged on percussion but neither the spleen nor the liver were palpable. There was moderate distention of the lower abdominal veins and slight pitting edema of the lower extremities.

Paracentesis yielded 2 to 3 liters of bile-stained fluid. The mental condition progressed in severity and just before death tonic convulsive seizures and Cheyne-Stokes respirations occurred. A bilateral Babinski and ankle clonus more marked on the left was noted. The temperature was practically flat throughout the course; on admission it was 99.8, and on exodus 98.8.

The blood count taken twice showed 17 to 19,000 white cells, with 80 to 87 per cent. polymorphonuclears; red blood cells five million, 85 per cent. hemoglobin. The urine contained a heavy trace of albumin, hyaline and granular casts and red blood cells; the patient was, however, menstruating. No leucine

* Presented December 11, 1924.

or tyrosine crystals were found. A spinal tap showed clear fluid without increased pressure; eight cells, globulin negative, sugar present. The blood Wassermann was anti-complementary; the spinal fluid Wassermann negative, the colloidal gold curve was 233211000, interpreted as weak paretic. The total bilirubin in the blood was found to be 588 mg. per 100 c.c.

Clinically the case was considered to be an acute poisoning of the liver of unknown cause and included the consideration of acute yellow atrophy, secondary and tertiary syphilis, infectious jaundice, salvarsan or arsenic poisoning.

An autopsy was performed with the following findings: There was marked jaundice of the skin and organs of the body. Old pigmented and indurated scarred areas of the thighs and arms indicated the habitual use of the hypodermic needle. The meninges were congested and edematous. The right lung was completely collapsed by hydro-thorax. Petechial hemorrhages were scattered over the pericardium and visceral peritoneum. Moderate ascites was present. There was a bilateral hydro-salpingitis and menstrual uterus.

The liver was markedly contracted, weighing only 920 gm.; the right lobe representing over three fourths of the entire organ. Thickenings of the capsule gave it a somewhat lobular appearance, the so-called *hepar lobatum* of tertiary syphilis. Scattered over the capsule were small elevated yellowish-white nodules, rubbery in consistency; 0.5 to 1 cm. in diameter. Long slender edematous and hemorrhagic fibrous adhesions stretched from the superior surface to the diaphragm giving the impression that they had been drawn out by a recent reduction in the size of the liver. On section the surface was grayish-pink, finely and diffusely fibrous. No normal lobulations could be made out. The nodules described above were strikingly confined to the capsule, invading the parenchyma only a few millimeters. There were many minute flecks of yellowish color scattered through the parenchyma and here and there small stellate areas suggesting cicatricial contraction. The gall bladder contained hydropic fluid. The mucosa was slightly edematous and intensely injected. The lymph nodes along the common duct were all enlarged, 1 cm. in cross section and showed a mottled reddish-yellow surface.

The spleen weighed 300 gm. Its capsule was smooth and tense. On section the surface was brick red, firm, with indistinct follicular markings. The interstitial tissue appeared increased.

The microscopic study of the liver reveals an extremely interesting picture. True liver cords as such are not to be seen, for everywhere the liver cords are broken up by an intense fibroblastic proliferation; and in respect to this the connective tissue may be here well vascularized, embryonal in type; or lacking capillarity, older with well-marked extra-fibrillary substance. The liver cells are vacuolated with a finely granular cytoplasm giving a reaction for neutral fats and fatty acids with the Nile blue sulphate stain; the nuclei are faded or fragmented.

Again there are many miliary areas ranging from simple collections of mononuclear cells to areas with necrotic centers sometimes containing hemorrhage, surrounded by a zone of epithelioid and mononuclear cells, in a mesh of connective tissue. Giant cells of the Langhans type are present but few in numbers. Plasma cells, mast cells and Russell's fuchsin bodies are to be noted. Eosinophiles and polymorphonuclears are infrequent. The biliary ducts are scattered irregularly throughout the sections, attempts at regeneration being questionable. Stains for the spirochete by Levaditi and Warthin and Starry silver agar methods have been doubtful.

The spleen histologically shows an increase in the fibrous tissue and the lymph nodes referred to above as enlarged show the presence of miliary gummata.

In a search through the literature, no cases have been discovered similar to this, exhibiting as it does a rapidly fatal course with symptoms referable to acute hepatic disease and presenting at autopsy a diffuse sclerosis with miliary gummata, a tertiary manifestation of syphilis. It is clinically similar to those cases of acute yellow atrophy of the liver arising in syphilitics at the time of the secondary rash, in the condition known as *icterus gravis syphiliticus* or *præcox*,¹ but here the similarity ends.

The essential etiological factor does not require discussion for the condition is admittedly syphilitic; but a brief résumé of some of the features of tertiary syphilis of the liver would not be out of place in consideration of the fact that clinical recognition is rare.

The condition is one of adult life. In the Bellevue series, Symmers² found 72 per cent. of the cases coming to autopsy were between the ages of twenty and seventy. The largest number in one decade were between the ages of thirty and forty. Clinically McCrae's³ highest decade was between the ages of thirty-one and forty. He also states that tertiary syphilis of the liver is fully as common as tertiary syphilis of the nervous system. Males are about twice as frequently affected as females. Increased frequency in the colored race has been noted but is probably due to social pressure.

Alcohol is considered a predisposing factor, notably by McCrae, who thinks it prepares the liver for subsequent involvement; not however on a basis of preceding cirrhosis. Sixty-

five out of his seventy cases used alcohol freely. Gerhardt⁴ called attention to the high incidence of granular degeneration of the kidney in the alcoholic cases and considered this as added proof of its toxicity. Other observers consider its effect as negligible.^{5, 6, 7}

Tertiary syphilis of the liver may be classified as diffuse or circumscribed. The diffuse form shows widespread infiltration and miliary gummatous accumulations. The circumscribed form consists of isolated infiltration and larger gummatous areas. Combinations of these occur; both forms leading to cirrhosis. Amyloid degeneration and suppuration of the gummata are among the rarer features.

The liver is enlarged in about half the cases; is firm and uneven; it may however be atrophic or broken up by cicatrizations into lobules, the botryoid or so-called *hepar lobatum*. This last form occurred in 16 per cent. of the Bellevue series. Sometimes it manifests itself in the form of Laennec's cirrhosis of the liver; a series of such cases having been reported and discussed by Symmers in 1917.⁷ Perihepatitis is also very constant and the frequent gummatous involvement of the suspensory ligaments led Virchow to attribute this predilection to trauma.

The clinical diagnosis is difficult not only by virtue of concomitant disease, such as arterio-sclerosis, nephritis and tuberculosis, but the onset from the time of the original infection may be from two to forty or more years. Again the symptoms of onset are rather general, some loss of weight which at times may be extreme, recurring pain in the upper abdomen, and gastrointestinal upsets. The most frequent complaints are swelling of the abdomen, pain in the abdomen, loss of weight, vomiting and fever sometimes accompanied by chills.

The liver may or may not be palpable. If palpable, limitation or fixation of its respiratory movement is considered significant. In the event of a coarsely nodular surface or extreme irregularity due to cicatrization, it may be mistaken for malignancy. However palpability of the spleen is a most constant finding and may be considered as decidedly against the diagnosis

of new growth. Malignancy and syphilis of the liver are also rarely co-existent.⁵ It is also to be noted that the splenic enlargement is quite definite in the majority of cases and places the condition in the toxic-infectious liver-spleen group. Hence splenic symptoms may obscure the hepatic disease. Osler⁶ describes three cases of syphilis of the liver with a clinical picture of Banti's disease.

Pain is often a prominent symptom and is caused by the peri-hepatic adhesions. It varies in intensity from a sense of pressure or weight in the abdomen to severe pain in the right upper quadrant radiating to the right shoulder. It may suggest gall bladder disease.

Jaundice is considered rare by Rolleston.⁹ It occurred in over half of McCrae's cases and in 28 per cent. of the Bellevue series. It is much more frequent in other forms of cirrhosis. True obstructive jaundice has been attributed not only to the encroachment of gummata upon biliary radicles, but to the pressure of the enlarged hepato-duodenal lymph nodes which are often hyperplastic and even gummatous.

Ascites is more often present in the atrophic and lobulated or intensely scarred forms. In general, however, it appears to occur regardless of the condition of the liver, owing to extra-hepatic features, such as perihepatitis, pachy-peritonitis and portal involvement.

Fever is variable and usually ranges to 101. It sometimes is accompanied by chills. It may be typhoidal or absent altogether.

The blood picture is one of slight or moderate secondary anemia. The differential count shows nothing of significance. Intractable diarrhea and gastro-intestinal hemorrhages may occur.

McCrae gives an interesting résumé of the causes of mistaken diagnosis which briefly are these:

The hepatic disease may be missed entirely by virtue of a cardiac lesion, the enlargement of the liver being attributed to chronic passive congestion or by virtue of a long continued temperature considered to be tuberculous in origin.

Abdominal disease recognized but thought to be due to malignancy or tuberculous peritonitis.

Hepatic disease recognized but undetermined and attributed to ordinary cirrhosis, abscess or gall stones; the last two causing useless surgical intervention in many cases. Cumston¹⁰ has reported such a series.

McCrae also calls attention to the frequency of left lobe involvement, always suggestive of syphilis; that ascites disappearing spontaneously or after paracentesis to reappear at some time later should excite suspicion; and also to the rapid disappearance of the fever and the reduction in liver size under the therapeutic administration of iodides.

The prognosis is considered favorable if an early diagnosis is made and specific therapy instituted.

It has been sought to present in this paper a case of acute miliary gummatosis of the liver, a tertiary manifestation of syphilis, ending fatally in eleven days, with a course not distinguishable from acute yellow atrophy, and to present briefly some of the clinical and pathological features of a disease too frequently undiagnosed.

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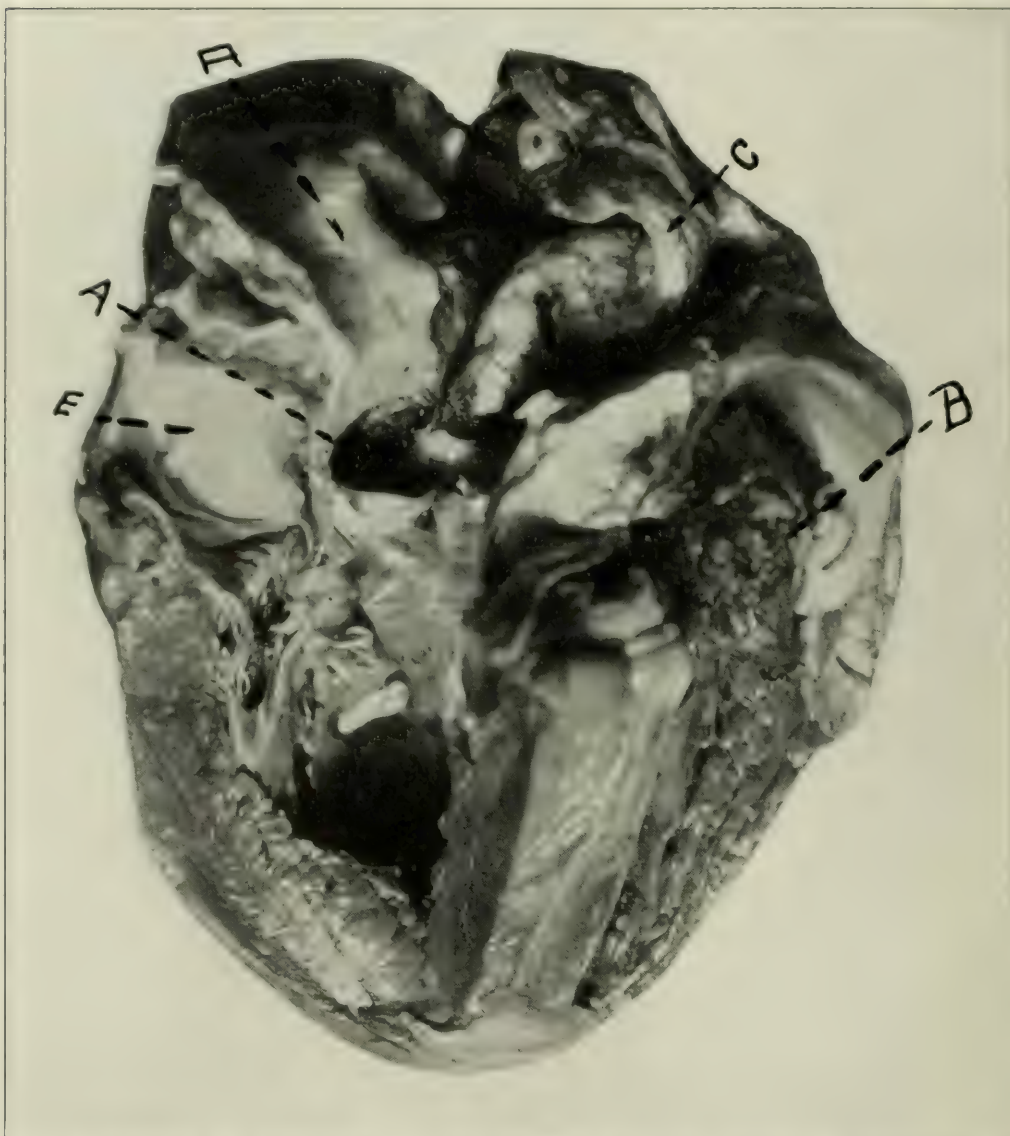
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AN UNUSUAL ANEURYSM OF THE AORTA *

G. L. ROHDENBURG, M.D.

(From the Pathological Laboratory, Lenox Hill Hospital, New York City)

The specimen is presented first because of the unusual location of the aneurysm, and second, as a demonstration of far advanced pathological change in a heart with but few clinical signs.



A, opening of aneurysm; E, left auricle wall; A, aorta; C, thrombus in aorta; B, thrombus in right auricle. Aneurysmal sac situated on posterior wall and not shown.

* Presented December 11, 1924.

The patient, a male sixty-five years old, was a coal-passer who had been working at his trade, if it may be so-called, up to within five days of his death. Twenty-four hours before admission to the hospital he had a chill, with a sharp rise in temperature, and pain on breathing, over the right side. A clinical diagnosis of pneumonia was made, which was confirmed by roentgen examination, all three lobes of the right side being involved. Death occurred four days after admission, in coma. The *x*-ray examination showed an enlarged heart, and physical examination disclosed a systolic murmur over the aortic region.

Post-mortem examination confirmed the presence of a right-sided pneumonia involving all three lobes, and aside from the cardiac lesion was without important deviation from the normal. The heart, when first removed, weighed 1,200 gm., the great weight being in part due to the large amount of blood in all of the dilated chambers. In the right auricle there was a firmly attached and organized thrombus situated in the appendage and measuring 5 cm. in its greatest diameter. The aorta showed a considerable degree of atheroma. Situated just behind the external cusp of the aortic valve and in the sinus was a smooth circular hole, 3 cm. in diameter, from which projected an organized thrombus which extended up to the arch of the aorta. When this thrombus was broken off at the opening in the aorta a cavity about 6 cm. in diameter extending down to the auricular ventricular groove on the left side was found. This cavity was filled with laminated and organized blood clot. The condition is shown in the accompanying photograph.

Aneurysms are, of course, still common enough, but it is believed that the present specimen is unique in its location.

AN ACCESSORY LIVER ATTACHED TO THE GALL BLADDER *

G. L. ROHDENBURG, M.D.

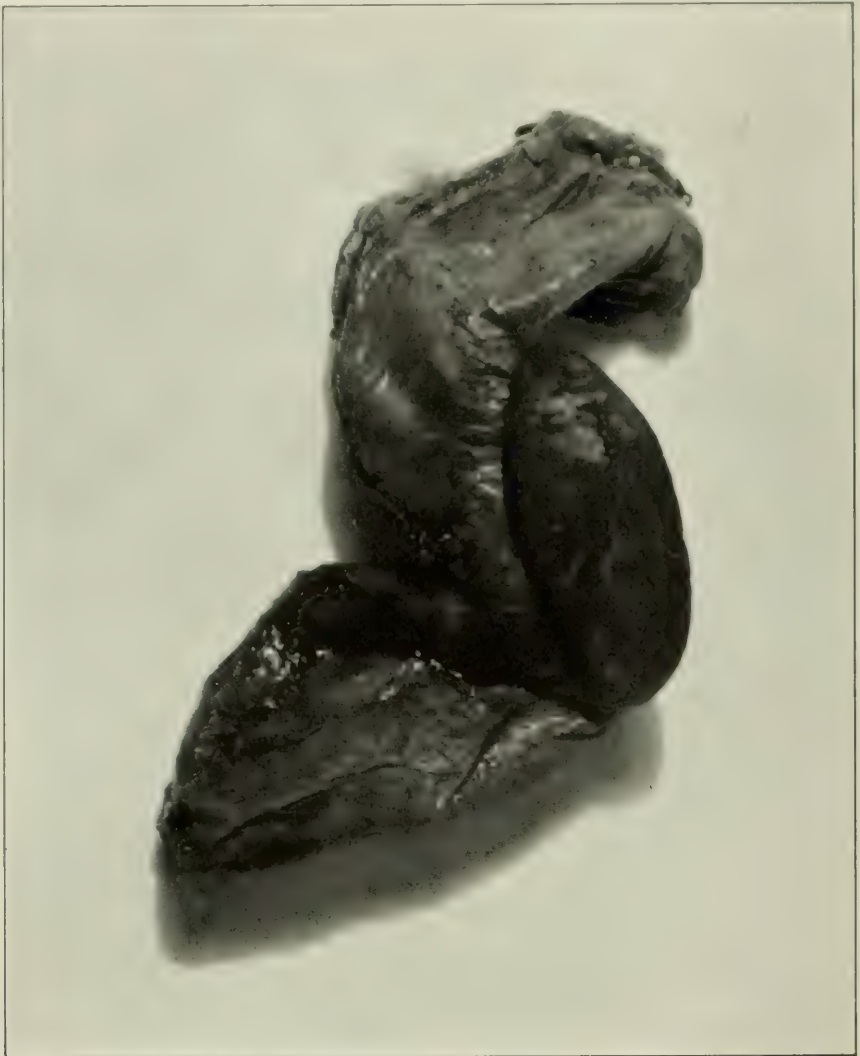
(*From the Pathological Laboratory, Lenox Hill Hospital, New York City*)

Malformations of the liver are not common, and are not of any great significance. For purposes of statistical data, however, they should be placed on record.

The specimen illustrated in the accompanying photograph was removed from a male, aged forty-five, who presented the usual clinical picture of an acute cholecystitis with calculi. The gall bladder was found to be congested and distended with many small calculi. It measures 5 cm. long, and when

* Presented December 11, 1924.

distended, 4 cm. in diameter. Attached to the ventral surface of the viscus and free from any attachment to the liver proper is an ovoid brown mass identical with liver tissue in the gross. This mass is 2.6 cm. long, 1.4 cm. wide, and 0.5 cm. thick. It is attached to the gall bladder wall by a broad but delicate pedicle. At about the center of its free surface is a depression through which enters a blood vessel of fair diameter, derived from the main artery of the gall bladder.



Photograph of gall bladder with liver attached

Discussion:

DR. PLAUT: I am very interested in the piece of liver attached to the gall bladder. It is a confirmation of the modern theory of development of the gall bladder. Ivar Broman¹ claims with good proofs that the gall bladder is not an outgrowth of the bile ducts, but that it is merely a part of the liver anlage

¹ Broman, I., *Upsala Läkaref. Förh.*, 1921, xxvi, 1.

which has remained in the cystic stage and has not developed into real liver tissue. Looking at the comparative anatomy, we find peculiar differences concerning the gall bladder of animals which are very nearly related to one another. Pigs, for instance, have a gall bladder, but one kind of them, the small peccary, has none; on the other hand, the cervidæ have no gall bladder, but the primitive moschus deer has one; it is similar with the rat and the mouse, and many other mammals. The giraffe in some cases shows absence of a gall bladder; in other cases, there has been one. It would be rather hard to explain these differences with the usual theory of gall bladder development. I see much less difficulty when applying Broman's hypothesis. To be sure, many of you have seen the gall bladder partly surrounded by liver tissue, especially near the tip. Such cases form transitions to the unusual finding which Dr. Rohdenburg has demonstrated.

PATHOLOGICAL CONDITIONS ASSOCIATED WITH THE PRESENCE OF FUSIFORM BACILLI AND SPIRILLA *

G. L. ROHDENBURG, M.D.

(From the Pathological Laboratory, Lenox Hill Hospital, New York City)

That fusiform bacilli and their associated spirilla may be the etiological agents in severe lesions of the mouth and throat has been recognized since the original report of Plaut and Vincent, whose names incidentally are now commonly given to the two organisms in question. That these same organisms are also associated with lesions in other portions of the body is perhaps not such common knowledge. It is the purpose of the present report to record several instances of the latter type.

Little need be said of the morphology of the organisms. Both types are found together, either the fusiform bacilli or the spiral form dominating as the case may be. A pure culture is a rather difficult thing to obtain, only the fusiform bacilli growing and then only in anærobic media. They are of rather slow growth, and the cultures have the characteristic foul odor frequently associated with their presence in mouth lesions. The spiral form has not been successfully cultured, and the exact significance of this form is still a matter of dispute. Cultures of

* Presented December 11, 1924.

the bacilli, even when injected in large doses intravenously, have in our hands been non-pathogenic for guinea pigs and rabbits, and after such injections we have not been able to recover the organisms from the tissues of the injected animal.

The most frequent site of infection by these organisms is the gingival portion of the mouth, with the tonsil and peritonsillar regions next in order of frequency. When the lesion is situated in the gum, it becomes spongy, exudes pus at times, and bleeds rather freely. Smears made of the secretion expressed by gum massage abound in the organisms and furnish an excellent source for cultural material. Occasionally the breath becomes foul. There are but few, and perhaps no, constitutional symptoms.

When the site of infection is in the neighborhood of the tonsil or on the tonsil itself, the clinical picture is that of a diphtheria. At times, however, the characteristic foul odor gives a clue as to the origin of the membrane. We have repeatedly observed cases in which the clinical diagnosis was diphtheria, although repeated cultures properly taken were negative, as for example in the following instance:

A male, aged thirty-five, was admitted with a temperature of 102°. A foul, greenish membrane covered both tonsils, the uvula, and the mucous membrane of the descending ramus of the jaw on both sides. He had been ill for seven days, and although four cultures were negative for diphtheria, he had been given 50,000 units of diphtheria antitoxin without appreciable effect upon the disease. The peculiarly foul odor suggested a possible Vincent's infection, and a smear of the membrane confirmed the suspicion. Recovery promptly followed local treatment with tincture of iodine and the intravenous administration of neosalvarsan.

Attention has repeatedly been called to the similarity between the condition of diphtheria and Vincent's infection. It has been a good plan in our experience to make a smear of the membrane in every case where a culture is taken, both culture and smear being taken at the edge of the lesion. A culture negative for diphtheria and a smear positive for Vincent's organisms settle the question. The smear is best stained by fixing with heat and using cold carbolfuchsin for a period of five minutes.

Another point of interest in this connection is the not infre-

quent blood picture which may accompany, but more often follows, a Vincent's infection of the throat. There is a leucocytosis sometimes as high as 50,000, with a marked increase in the lymphocytes reaching at times as high as 80 per cent. and simulating in every way a true leukemia, but with the difference that all spontaneously recover, as in six cases observed by us in one epidemic. In one instance the blood picture simulated leukemia over a period of a year. Accompanying the blood changes in the six cases observed was a general increase of the lymphoid tissue and a splenic enlargement.

Our present interest is more centered in pulmonary infections by these correlated organisms. The Italian school has described the condition in considerable detail within the past five years, and in addition, several isolated case reports have appeared in the American literature. The group of cases cited here has not been previously reported.

CASE 1. The patient was an Italian male, aged twenty-three. One day before coming under observation he had a chill, with a sharp rise in temperature, and pain on the left side of the chest. Physical examination revealed a circumscribed patch of flatness in the axillary line, with bronchial breathing and many crepitant râles. The diagnosis of pneumonia was made. The temperature continued for three days, the physical signs gradually advancing so as to include the entire lower lobe. It had been noted from the first that the sputum was frothy, brightly stained with blood, unusually foul, copious, and unlike typical pneumonic sputa, it was not mucilaginous. Smears of the sputum showed many spirilla with only an occasional fusiform bacillus in evidence. Dark field examination showed the organisms to be actively motile. The condition was then recognized, and the patient given intravenously on three occasions at intervals of forty-eight hours an arsenic preparation. The temperature became normal within twenty-four hours after the first injection; the physical signs remained for almost a week, and the sputum contained a few spirilla six weeks after the temperature was normal. During the course of the fever there was a leucocytosis of 22,000, of which 73 per cent. were lymphocytes. The blood Wassermann test was negative. The blood count had not fully returned to normal six weeks after the cessation of the temperature, showing 16,000 white cells with 54 per cent. lymphocytes.

CASE 2. This patient was a German, aged fifty-six, with a history of repeated attacks of bronchitis coming on at apparently regular intervals of about twenty-one days, over a period of six years. The acute attacks lasted about seven days, and were not influenced by treatment. They were characterized by violent attacks of coughing, with but little sputum and much wheezing. The

physical signs during the attacks were those of a chronic bronchitis and emphysema, while between attacks there were no indications of an abnormal condition in the chest. Repeated x-ray examinations of the chest were negative. Examinations of the sputum were negative for tubercle bacilli, but numerous Vincent's organisms were found during the height of the attacks. Many pockets containing similar organisms were found about the teeth. The treatment consisted of injections of atoxyl, extraction of the teeth, and the use of an arsenic mouth wash. Recovery promptly occurred, and for the past two years there has been no recurrence.

CASE 3. A female, American, aged fifty-five, gave a past history without interest except for a panhysterectomy five years ago for an early carcinoma of the fundus. Suddenly and without premonitory symptoms an asthma developed, accompanied by distressing cough of paroxysmal character. Coughing attacks occurred at intervals of ten to fifteen minutes, lasted five or six minutes, and kept up in this fashion six weeks without intermission. The loss of weight during this period was almost half the previous total body weight. The physical signs were those typical of an acute asthmatic seizure. Contrary to expectations, none of the usually applied procedures gave even temporary relief, adrenalin and morphine being included. X-ray examination of the chest was negative; pulmonary metastases were not demonstrable. There was no fever, and the blood count was normal. The scanty sputum was tenacious and ropy, but not blood-stained.

Protein sensitization tests were negative with food proteins, bacterial proteins, as well as pollen proteins, and in all tests were made with ninety-four different proteins. Examination of the sputum was negative for tubercle bacilli. After the six weeks period of acute symptomatology, the clinical picture changed in the following sequence. The asthmatic symptoms rapidly cleared; the cough became looser and then quite suddenly ceased. There followed a period of freedom from all symptoms and then the entire course was repeated: severe asthma for two days, severe cough for three days, then six days of relative or absolute freedom from all symptoms, and then again another attack, the cycle being from eleven to thirteen days. This kept up for approximately three months. All types of examination, some logical, others frankly foolish, were made, without revealing a clue as to the etiology. The sputum was then examined for Vincent's organisms, and a large number were found, the fusiform bacilli predominating during the asthmatic portions of the seizures, while the spirilla predominated during the coughing attacks.

Treatment with arsenic as arsenious acid was commenced, and after four weeks complete recovery followed, the patient remaining perfectly well for a period of eight months. Then there was a sudden recurrence of all the previous symptoms. The physical signs were the same as those previously noted, and the sputum examinations again showed the Vincent type of organisms, but this time the asthmatic seizures were longer, the cough less, and arsenic had little or no effect. Observations showed that during the asthmatic periods the sputum bacteria consisted of streptococcus viridans, staphylococcus aureus hemo-

lyticus, and the fusiform bacilli, spirilla being very few and far between. The coughing attacks, as has just been stated, were much shorter and lasted but one or two days, and during them the spirilla were the dominant organism. The three organisms were grown and skin sensitization tests were made. A marked reaction followed the application of the fusiform bacilli; none occurred with the staphylococcus or streptococcus. A thorough re-examination of the teeth showed no focal infection with the organisms. The tonsils had been removed many years ago, and the tonsil beds were clean. A vaccine of the fusiform bacilli was prepared and administered in an initial dose of 100,000 bacteria, without bad effect. The dose was then increased in the usual fashion and arsenic as the cacodylate was given by injection. There was a prompt and rather striking cessation of all symptoms.

Taken together with the cases which have been reported in the literature, enough has been cited to emphasize the point that the organisms in question may be of much more pathogenic significance than is ordinarily thought to be the case. They should be searched for in every obscure pulmonary condition. They may be found where least expected, for we have been able to demonstrate them in a pleural exudate following a pneumonia supposedly due to pneumococcus. Arsenic is apparently effectual only in the stage in which the spirilla dominate the picture. No drug that we have tried has been effectual in the phase where the fusiform bacilli dominate. In one case where the fusiform bacilli dominated, a clinical improvement (the period is too short to speak of cure) followed the use of an autogenous vaccine of the fusiform bacilli. There are apparently several types of the organism with apparently particular tissue affinities, and the entire question is in need of extensive investigations, both from the bacteriological as well as the clinical standpoint.

Discussion:

DR. PLAUT: I think Dr. Rohdenburg's case is the first which shows spirilla and fusiform bacilli in a closed part of the body. They generally do not invade the deep tissue, and are found in connection with the external world. I have seen a number of local pulmonary infections due to the spirillum and the fusiform bacillus, but I never have seen a case of effusion in the pleura. I would like to ask if the fusiform bacilli were motile.

DR. ROHDENBURG: No motion except Brownian movement was observed.

DR. PLAUT: I have seen in many textbooks the statement that fusiform bacilli were not motile, but I have seen them in motion many times, and I have

had this confirmed by Professor Plaut, who is one of the best dark field workers. They are somewhat slow, but they go quietly through the field. I believe there is no doubt about their being motile.

DR. FELSEN: I would like to ask whether Dr. Rohdenburg has ever considered Vincent's organisms more or less as saprophytes. Some statements I think partly bear that out. I have noticed, for example, the spirillum and fusiform organisms frequently present associated with or following diphtheria, pneumonia, leukemia, and other debilitating diseases. They are very prone to occur in deep ulcers with small necrotic foci associated with any of the wasting diseases. In diphtheria they are prone to occur at the edge of the membrane. Another peculiar feature of these organisms is that they seem to possess varying degrees of virulence. In some patients a dentist will suspect the presence of Vincent's angina by a peculiar appearance about the gums, and although there is no ulceration in the mouth, if a smear be taken, one is surprised to see typical fields of fusiform bacilli and spirilla. I should like to ask Dr. Rohdenburg whether he would consider them secondary invaders, or primary agents, and as such should they be considered as etiological factors in a disease with distinct clinical entity.

DR. ROHDENBURG: I do not believe that they are always secondary invaders. We have of course the ordinary sore throat due to the streptococcus for example, but I must confess that I have never seen a sore throat of that type associated with such marked blood change. About thirteen or fourteen years ago we had an epidemic of Vincent's angina at the Lincoln Hospital. This went on for eight or nine weeks. The matron of the hospital, who had had an attack, presented herself feeling rather poorly. Physical examination showed a big spleen, and a blood count was done. The first conclusion drawn was that the patient had leukemia. I have seen a good many leukemias, but I never saw one that got well in six weeks without having anything done for it. We had thirty or forty cases at that time. These organisms do come in as a secondary invader, but there are also conditions in which they should be considered as the cause of the clinical entity present. I recall one case mistaken for diphtheria with such a severe infection that before it cleared up the larger part of the lower jaw came away as a sequestrum, and also all the upper and lower teeth. There was an amazing amount of antitoxin given this patient, in spite of the fact that everything was negative for diphtheria. He was practically moribund when he came into the hospital, and had to be put into the isolation ward, because of the odor. The diagnosis was made with one whiff, so to speak.

DR. PLAUT: Concerning the frequency of infections with fusiform bacilli and spirilla, it generally depends on the presence of men who are interested in it. When I came to Paterson, they were astonished to get repeatedly a diagnosis of Vincent's angina. They had very seldom had one before in the hospital. I never make a culture without looking at the smear first.

Concerning the question of their being secondary invaders, I found a solid field of spirilla and fusiform bacilli on a slide said to be made from an ear

swab. I thought that the labels had been mixed up. I took a fresh smear from the ear of the patient, and got the same picture. In this case of chronic otitis media, the smear was full of spirilla and fusiform bacilli. I looked at many slides from the throat, and found only an occasional spirillum, which is without significance. Certainly the chronic ear condition in this case was due to an anærobic streptococcus. I published that a few years ago, and six weeks later a second paper appeared on the subject. In 1913 Sims described the same condition, and it seems to me that the conditions in which fusiform bacilli are found are becoming more frequent.

DR. KLEMPERER: In the second case there was an *x*-ray taken which was negative. In all the other cases was the *x*-ray negative?

DR. ROHDENBURG: The roentgenograms were all negative, except the one of the patient with pneumonia. This showed the consolidation in the chest.

DR. KLEMPERER: You would consider these cases as chronic bronchitis?

DR. ROHDENBURG: Yes.

WELL-DEFINED RADIOLOGIC EVIDENCE OF CARCINOMATOUS METASTASIS IN BONE: REPORT OF A CASE *

PERCY BROWN, M.D.

The reader feels that he can best express his appreciation of the opportunity to appear before you by condensing his observations into the space of a very few moments, and by showing the radiographic record of a single case in illustrative exposition of the point he essays to take.

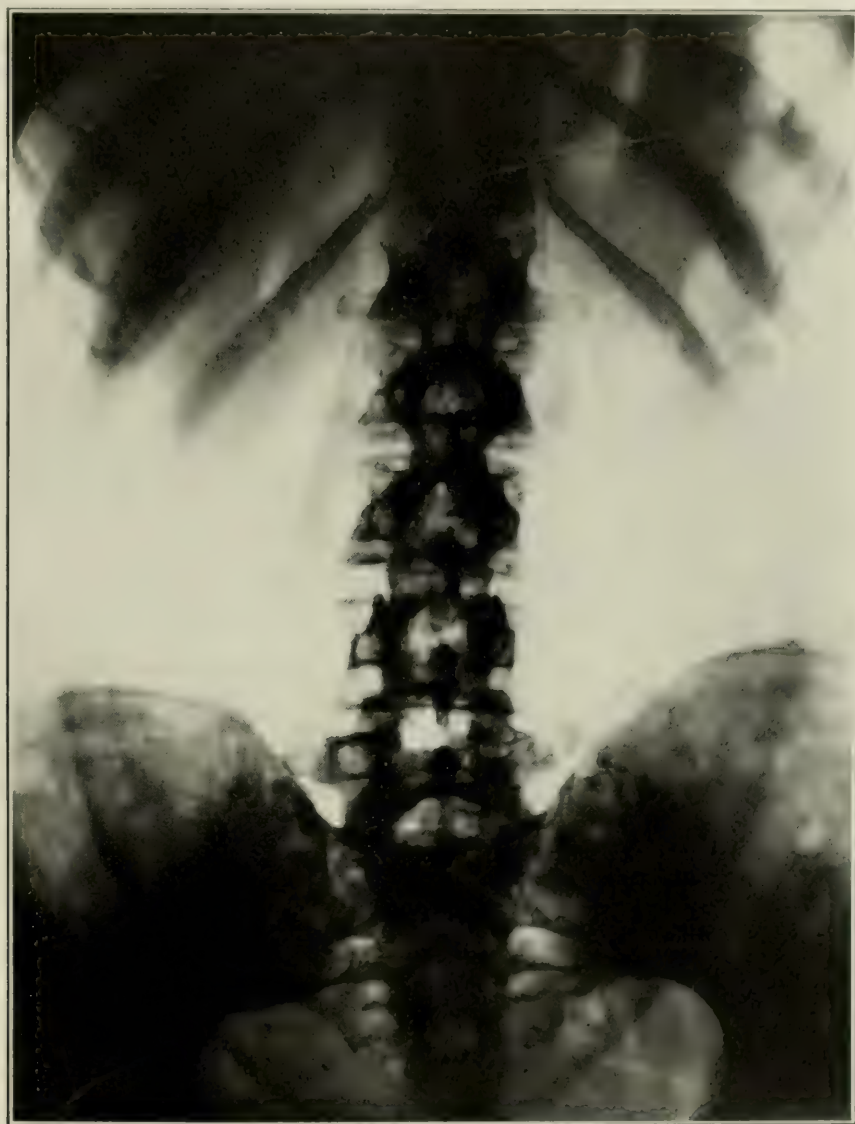
To realize the increasing support given by the authorities in Pathology to the *x*-rays of Roentgen as a coadjutant in the macroscopic diagnosis of metastatic bone lesions, one has only to peruse their latest writings. Such support has been and can be merited solely by more accurate technical effort on the part of those working in the radiological field. While the precision of the pathological laboratory in matters microscopic can never be attained, it is nevertheless true that roentgenology must regard such precision as an example constantly to follow, if she is to strengthen and amplify her own interpretation of morbid anatomy by the methods of revelation peculiar to her.

* Presented December 11, 1924.

From time to time disappointment has been expressed by clinicians in the apparent inexactness of *x-ray* demonstration of bone-carcinoma, or at least in the failure, at times, of *x-ray* evidence to correlate the shadow-complex revealed with the source, and consequently the type, of the metastasis. Such disappointment would not occur if the technical accuracies of *x-ray* investigation could always approach those of the pre-microscopical steps, if one may so term them, of the pathological laboratory—such as tissue-hardening, section-cutting and staining. In this connection a brief may be held for radiology in that its constant technical problems are those of the living tissue, with the subjective uncertainties of forced or painful posture or of involuntary visceral movement; on the other hand, a moment's thought will recall the fact that, in the *x-ray* laboratory, the technical effort to improve differentiation of shadow in soft and ill-contrasting tissues has resulted in the sacrifice of older and definitely established methods making for the beauty and the accuracy of detail. To borrow a simile from the microscopist, in our effort brilliantly to illuminate the field of our low-power, we forget the potentialities of our high-power.

In no form of radiologic work is the question of detail in the shadow-complex of greater importance than in the differentiation of bone-tumors in the living subject. Such differentiation often tends to hasten the tranference of the problem to the hands of the pathologist for ultimate decision, and thus life may be saved. If the roentgenologist uses his radiologic "high-power" as he should, and does not content himself by illuminating his low-power field merely, he should be prepared to inform himself as to these points with respect to bone-tumor: (1) where in the bone it originates; (2) in what tissue it may be at the moment of observation; (3) what may be the neighborhood reaction to its presence; and (4) the behavior of the normal barriers, that is to say, the non-proliferative barriers, in the face of its extension or advancement. Authors agree that at least two of these points should be clarified in the translation of the shadow-complex, and if this cannot be, it is usually due to technical deficiency.

The illustrative case herewith presented is one of diffuse carcinoma of bone, the primary source of which was mammary. The original tumor and its customary adnexa were excised in the month of June, and this radiographic record was obtained in



November. No x-ray evidence was acquired at the time of operation as to the possible condition of skeletal structure; the age of the metastasis, therefore, is indeterminate.

The characteristics and the arrangement of the bone lesions well illustrate the roentgenpathology of this type of tumor, and

the law of distribution is closely adhered to as well, in the exemplification of almost the entire gamut of the order of involvement: 1, ribs; 2, dorsal spine; 3, lumbar spine; 4, ilia and sacrum. Only the indisposition of the patient, who is still living, prevents an investigation of 5, 6, 7, namely, the great femoral trochanters, the skull, and the humeri. Early scapular changes are suggested, however, in another radiograph to be shown directly.

In all radiographic fields recorded upon films there is always what the reader terms the "central area of accuracy." Sometimes this is the center of interest; sometimes, unfortunately, it is not. But it always exists. It is the center of least divergence of the rays in combination with the center of closest approximation of film to the pathologic area. By no means does it always fall in the center of the field.

In the field before you it falls in the area of the lower posterior ribs, and thus there appears here, and here only, the degree of detail necessary for diagnostic accuracy. A scrutiny of the bone lesions within the vicinity of this central area of accuracy will reveal the fact that they follow the rule pertaining to the shadow-complex, as applied to bone, of carcinoma-metastasis of the epithelial type: (1) the locus of the process with relation to nutrient supply; (2) vacuoles clear of subsidiary shadows, denoting no bone-formation within the tumor; (3) no reactive hyper-production of bone in advance of tumor-progress, thus indicating rapid growth and extension, and (4) invasive involvement of the cortex by sheer absorption, without cortical distention or fragmentation.

Thus, the point of the matter outlined in these few words is this: the roentgenologist, to be a dependable co-worker in the great field of pathologic practice, must so direct his technical effort as ever to bring the center of pathologic interest within the central area of radiological accuracy. If this be done as consistently as is possible, there will be no great divergence in the results of all those who have been engaged upon the problem.

Discussion:

DR. CHRISTENSEN: I am interested to know if you find the occurrence of metastasis from other organs in the order that you mentioned.

DR. BROWN: Only from mammary cancer. A nomenclature in this order was applied originally to the various metastases of mammary cancer in the usual manifestation of this type.

DR. CHRISTENSEN: What was the age of the patient?

DR. BROWN: It was about forty-five.

One may perhaps say here that the prostatic type gives an entirely different shadow-complex, so that, under ordinary conditions, one should be able to make the differential diagnosis by the x -ray evidence alone.

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